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L4   ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:        2009:363181  CAPLUS
DOCUMENT NUMBER:         150:352196
TITLE:                   Preparation of pyrazinylpiperazinyl sulfones as
                         modulators of GPR119 activity
INVENTOR(S):             Alper, Phillip; Azimioara, Mihai; Cow, Christopher;
                         Epple, Robert; Jiang, Songchun; Lelais, Gerald;
                         Michellys, Pierre-Yves; Mutnick, Daniel; Nikulin,
                         Victor; Westcott-Baker, Lucas
PATENT ASSIGNEE(S):      IRM LLC, Bermuda
SOURCE:                  PCT Int. Appl., 234pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
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     WO 2009038974        A1    20090326   WO 2008-US75145        20080903
         W:  AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
             CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES,
             FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE,
             KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
             ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
             PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ,
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         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,
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             AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.:                     US 2007-974064P     P  20070920
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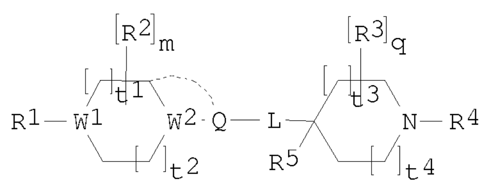

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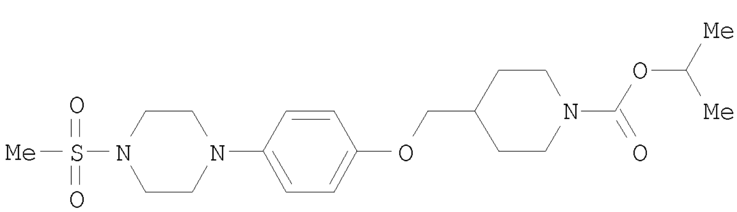


II

AB   The title compds. I [Q = a divalent or trivalent radical selected from (un)substituted (hetero)aryl and (hetero)cycloalkyl; W1, W2 = CR21, N

(wherein R21 = H, CN, alkyl, etc.); L = alkylene, alkenylene, (CH2)nO, etc.; n = 0-5; m = 0-4; q = 0-4; t1-t4 = 0-2; R1 = substituted sulfonyl; R2, R3 = H, halo, OH, etc.; R4 = R8, CO2R8 (R8 = alkyl, aryl, heteroaryl, etc.); R5 = H, alkyl, haloalkyl, etc.], useful for treating or preventing diseases or disorders associated with the activity of GPR119, were prepared E.g., a multi-step synthesis of II, starting from 4-(hydroxymethyl)piperidine and iso-Pr chloroformate, was given. Compds. I produced a concentration-dependent increase in an intracellular cAMP level.

I

show an EC50 of between 1 + 10-5 and 1 + 10-10 M (more specific data were given for representative I). Pharmaceutical compns. comprising compds. I and methods of using such compds. to treat or prevent diseases or disorders associated with the activity of GPR119, were disclosed.

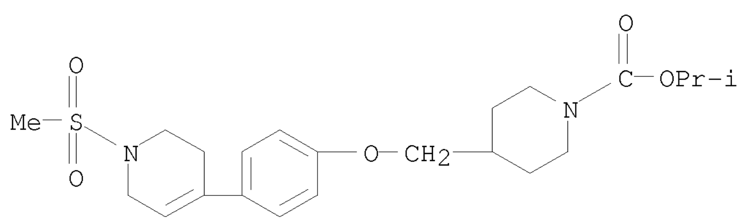
IT 1134105-21-7P 1134105-23-9P 1134105-25-1P 1134105-31-9P 1134105-33-1P 1134109-19-5P 1134109-58-2P 1134110-04-5P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of pyrazinylpiperazinyl sulfones as GPR119 modulators useful in treatment and prevention of GPR119 mediated diseases)

RN 1134105-21-7 CAPLUS

CN 1-Piperidinecarboxylic acid, 4-[[4-[1,2,3,6-tetrahydro-1-(methylsulfonyl)-4-pyridinyl]phenoxy]methyl]-, 1-methylethyl ester (CA INDEX NAME)



RN 1134105-23-9 CAPLUS

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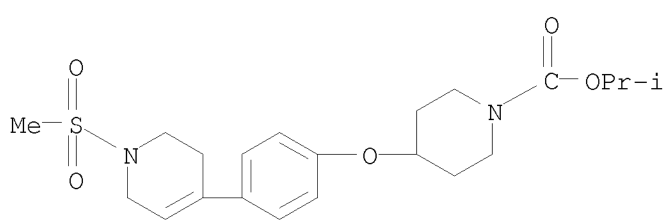

RN 1134105-25-1 CAPLUS

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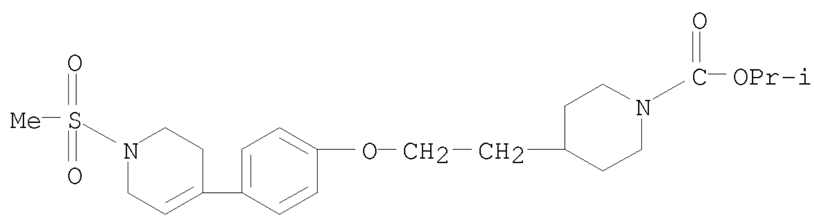

RN 1134105-31-9 CAPLUS
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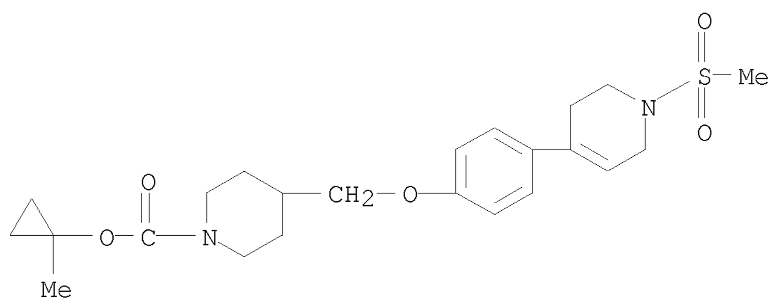

RN 1134105-33-1 CAPLUS
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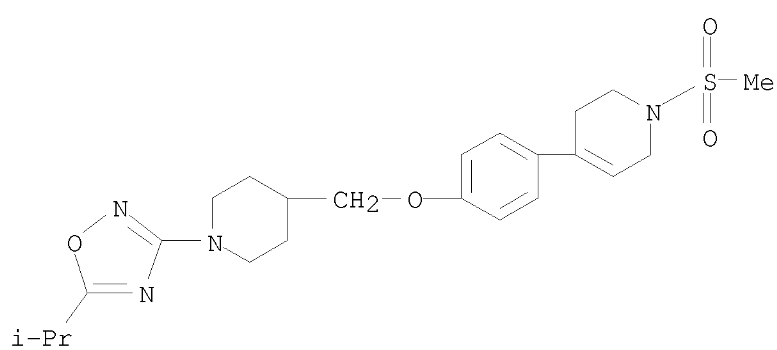

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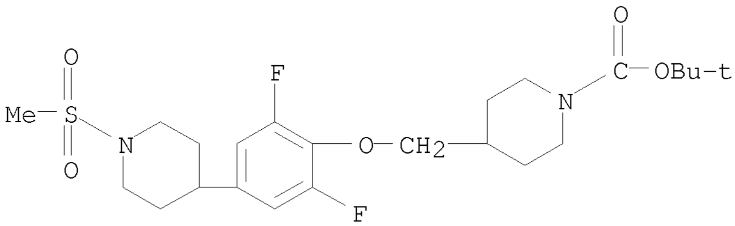
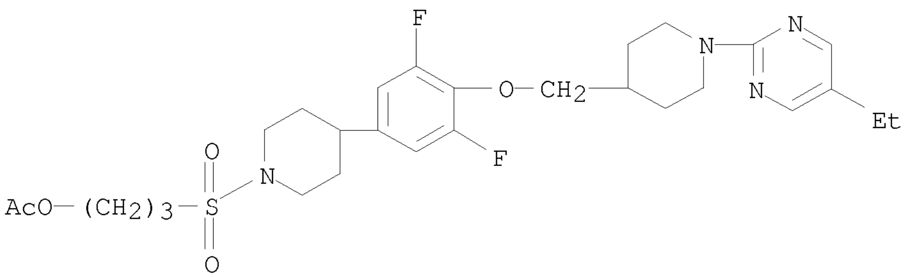


RN 1134109-58-2 CAPLUS
CN 1-Propanol, 3-[[4-[4-[[1-(5-ethyl-2-pyrimidinyl)-4-piperidinyl]methoxy]-3,5-difluorophenyl]-1-piperidinyl]sulfonyl]-, 1-acetate (CA INDEX NAME)



RN 1134110-04-5 CAPLUS
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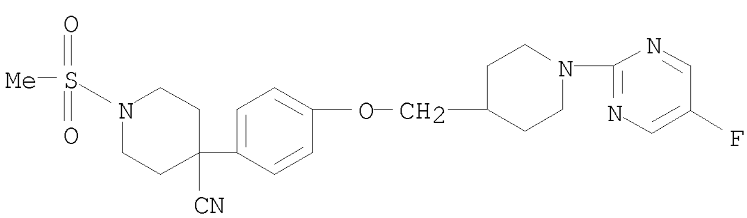

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1134105-48-8P 1134105-56-8P 1134105-58-0P
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1134105-66-0P 1134105-68-2P 1134105-69-3P
1134105-71-7P 1134105-73-9P 1134105-75-1P
1134105-77-3P 1134109-22-0P 1134109-25-3P
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1134109-37-7P 1134109-40-2P 1134109-43-5P
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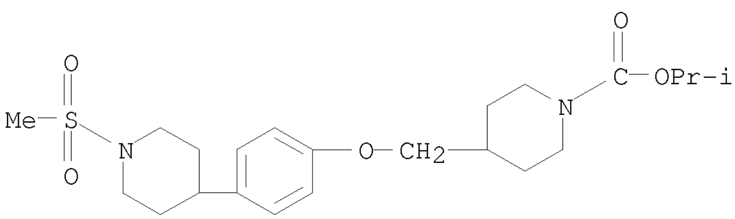
1134109-55-9P 1134109-60-6P 1134109-62-8P
1134109-65-1P 1134110-07-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrazinylpiperazinyl sulfones as GPR119 modulators useful in treatment and prevention of GPR119 mediated diseases)
RN 1134105-38-6 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[4-[1-(methylsulfonyl)-4-

piperidinyl]phenoxy]methyl]-, 1-methylethyl ester (CA INDEX NAME)



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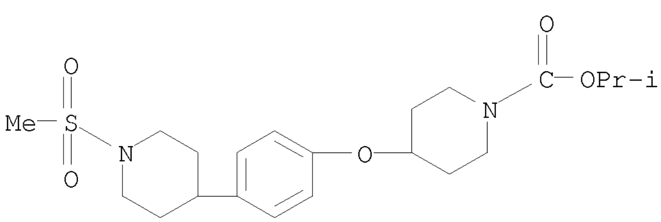

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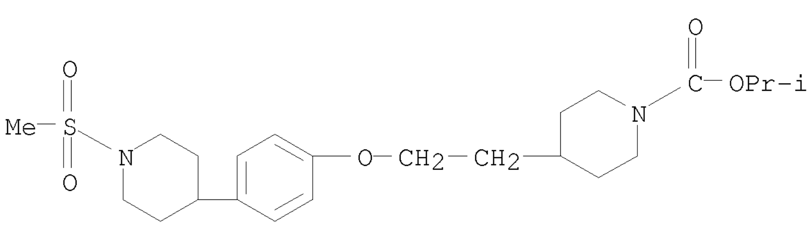
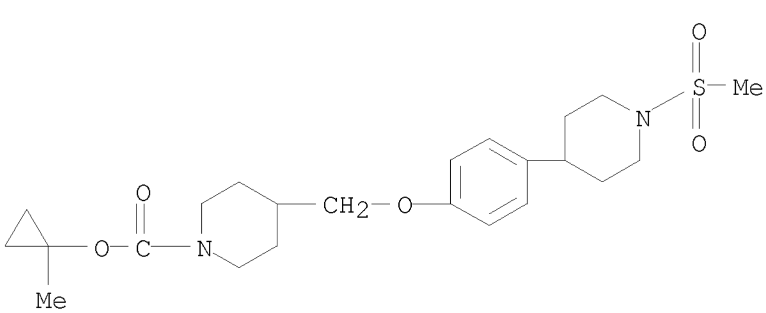
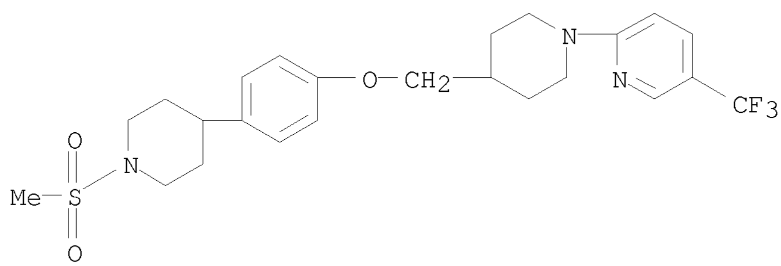


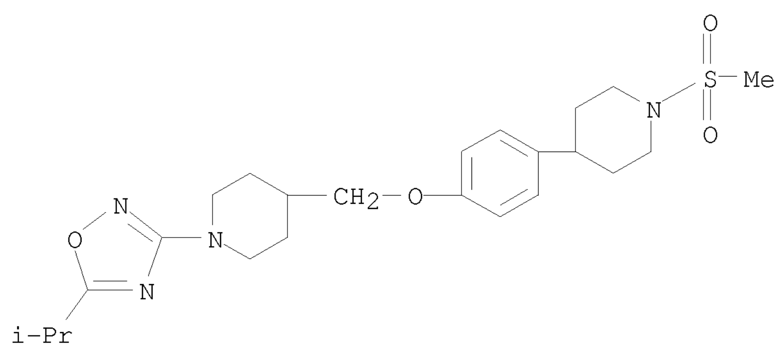
RN 1134105-48-8 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[4-[1-(methylsulfonyl)-4-piperidinyl]phenoxy]methyl]-, 1-methylcyclopropyl ester (CA INDEX NAME)



RN 1134105-56-8 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



RN 1134105-58-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



RN 1134105-60-4 CAPLUS
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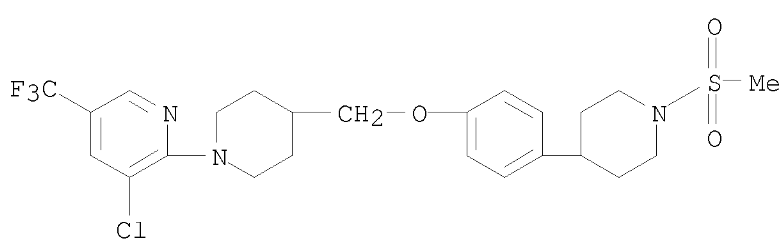

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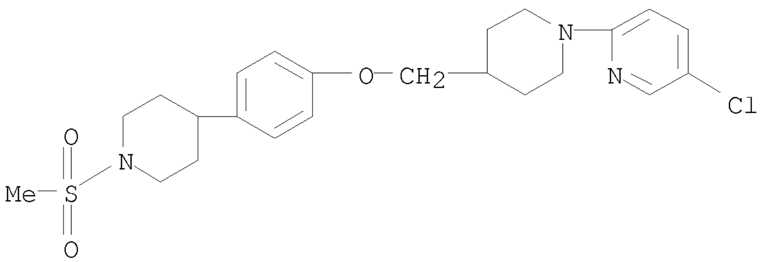
CN INDEX NAME NOT YET ASSIGNED



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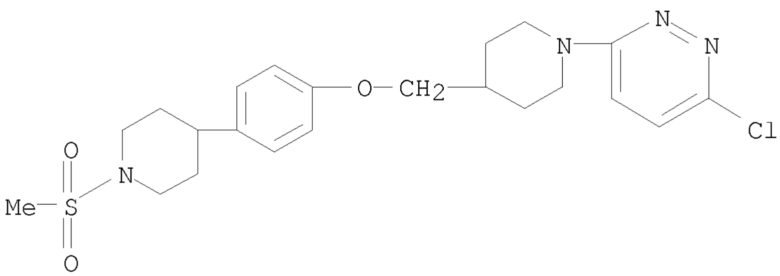
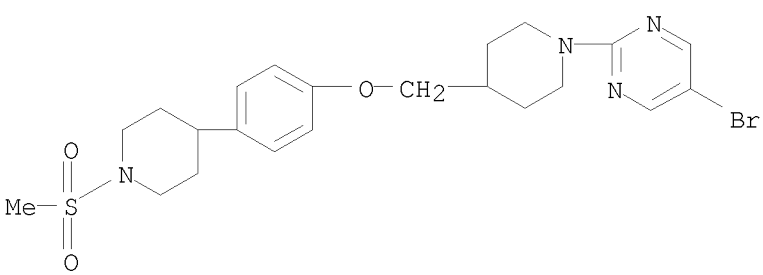


RN 1134105-66-0 CAPLUS
CN Pyrimidine, 5-bromo-2-[4-[[4-[1-(methylsulfonyl)-4-piperidinyl]phenoxy]methyl]-1-piperidinyl]- (CA INDEX NAME)



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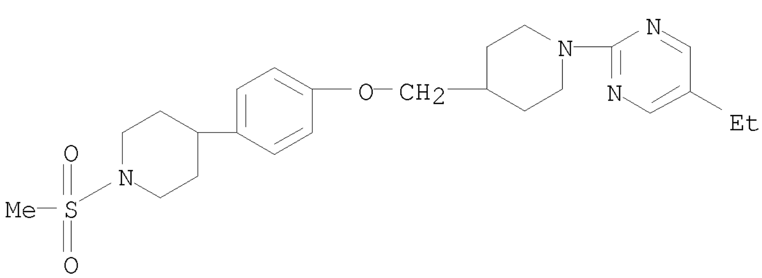
CN Pyrimidine, 5-ethyl-2-[4-[[4-[1-(methylsulfonyl)-4-piperidinyl]phenoxy]methyl]-1-piperidinyl]- (CA INDEX NAME)



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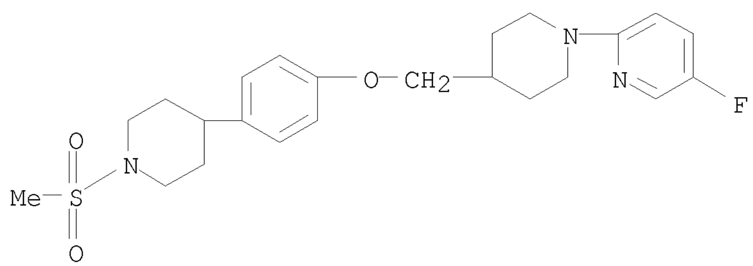
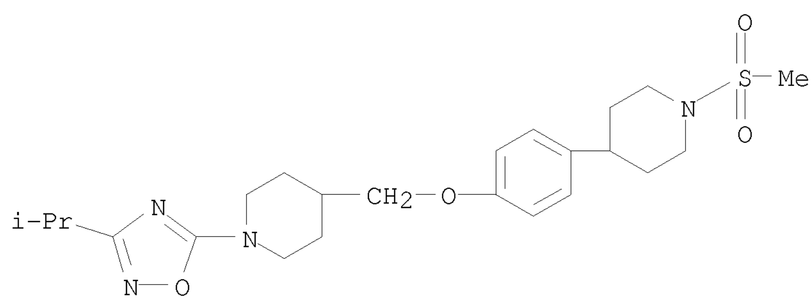
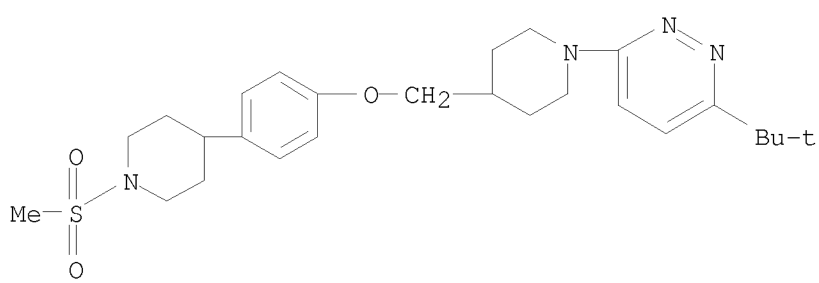
CN   INDEX NAME NOT YET ASSIGNED



RN   1134105-71-7 CAPLUS
CN   INDEX NAME NOT YET ASSIGNED



RN   1134105-73-9 CAPLUS
CN   Pyridazine, 3-(1,1-dimethylethyl)-6-[4-[[4-[1-(methylsulfonyl)-4-piperidinyl]phenoxy]methyl]-1-piperidinyl]- (CA INDEX NAME)



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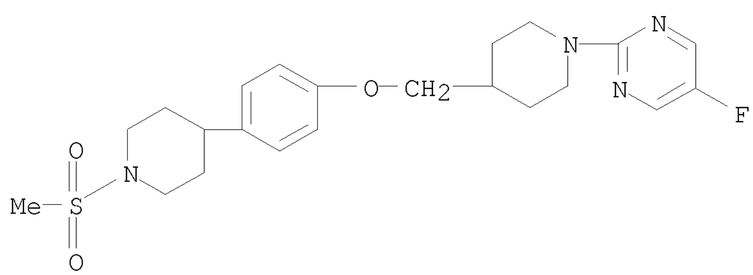
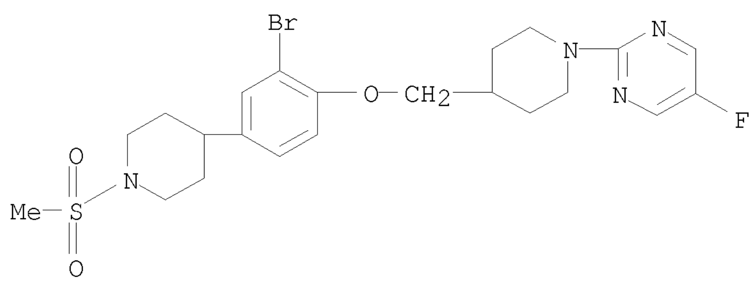
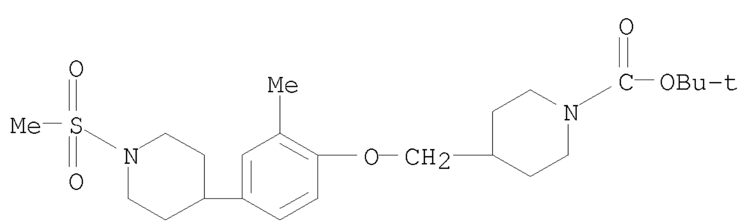


RN 1134105-77-3 CAPLUS
CN Pyrimidine, 2-[4-[[2-bromo-4-[1-(methylsulfonyl)-4-piperidinyl]phenoxy]methyl]-1-piperidinyl]-5-fluoro- (CA INDEX NAME)



RN 1134109-22-0 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[2-methyl-4-[1-(methylsulfonyl)-4-piperidinyl]phenoxy]methyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)



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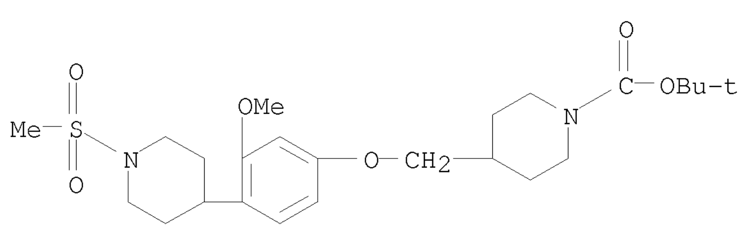

RN 1134109-28-6 CAPLUS

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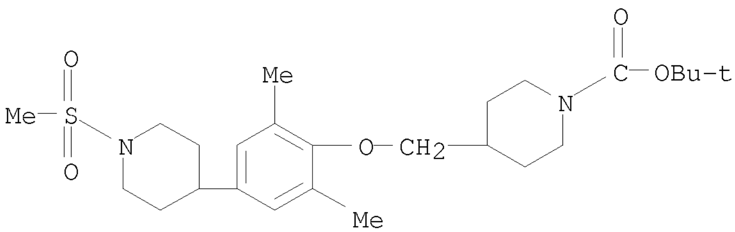
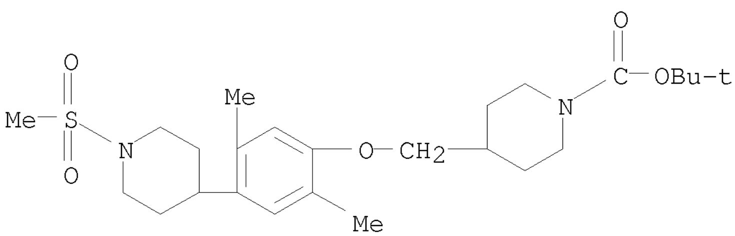


RN   1134109-31-1 CAPLUS

CN   1-Piperidinecarboxylic acid, 4-[[2,5-dimethyl-4-[1-(methylsulfonyl)-4-piperidinyl]phenoxy]methyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)



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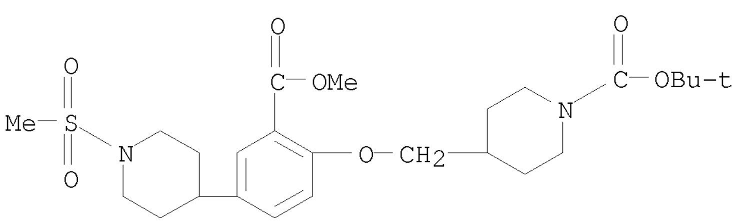

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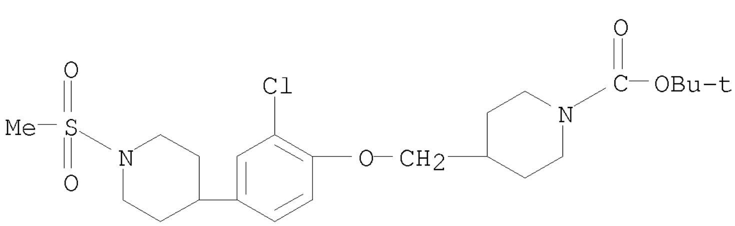

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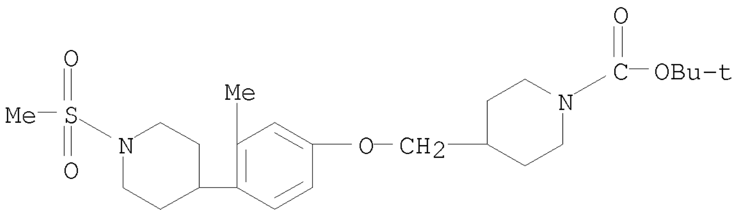

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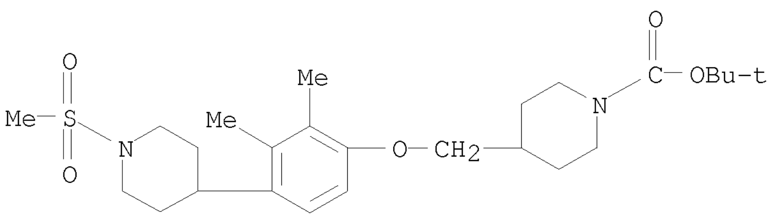

RN 1134109-46-8 CAPLUS
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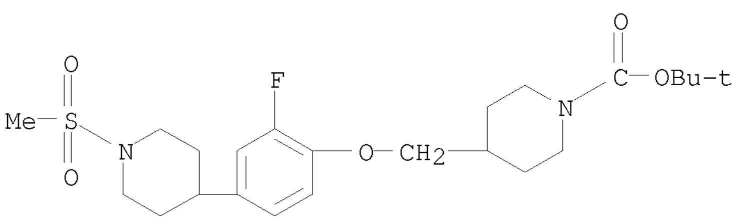

RN 1134109-49-1 CAPLUS
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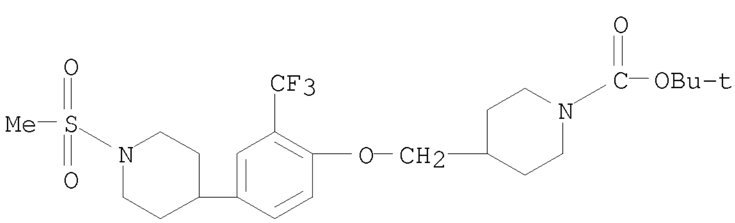

RN 1134109-52-6 CAPLUS
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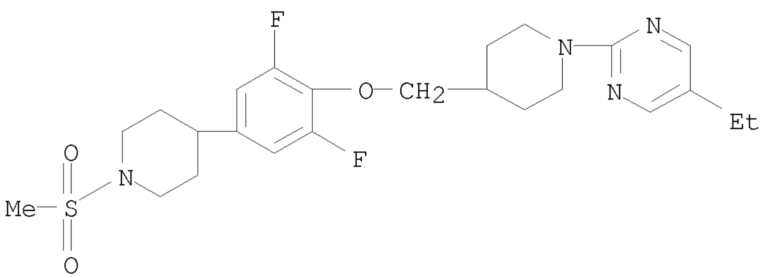

RN 1134109-55-9 CAPLUS
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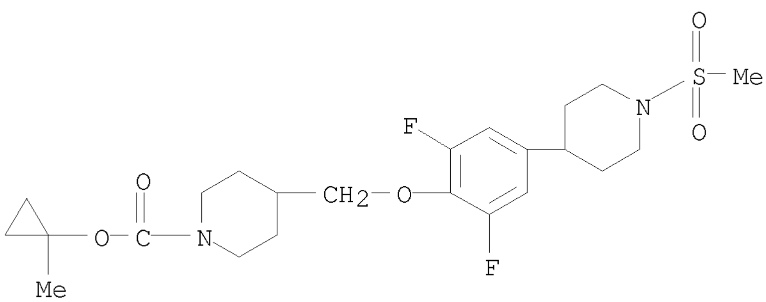

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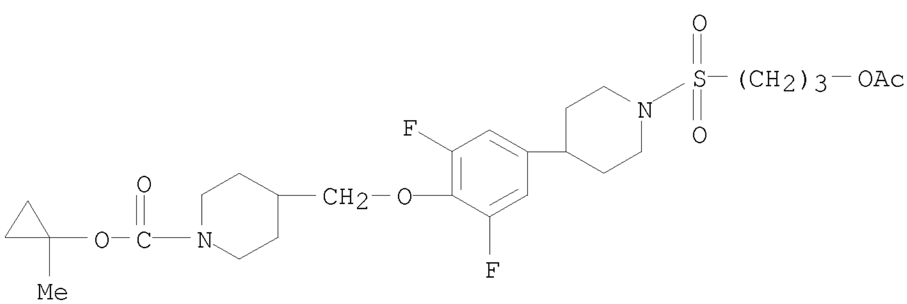

RN 1134109-62-8 CAPLUS
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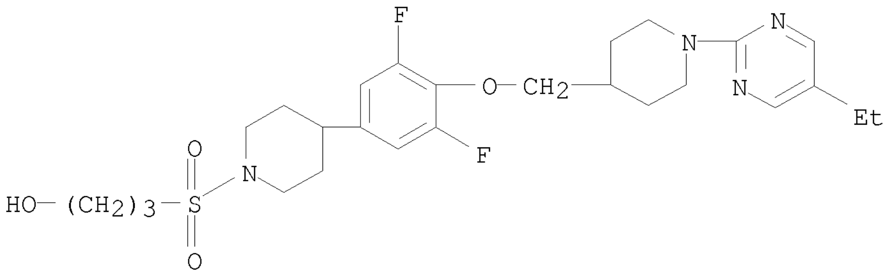
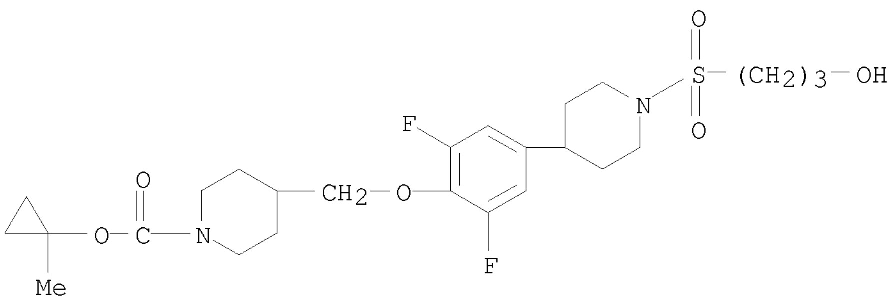
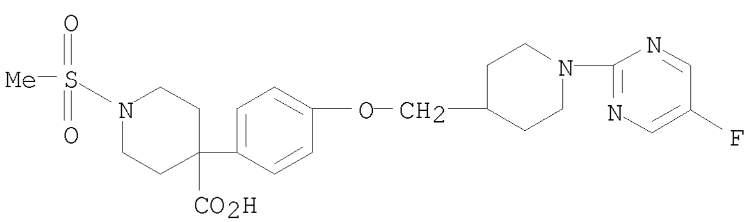


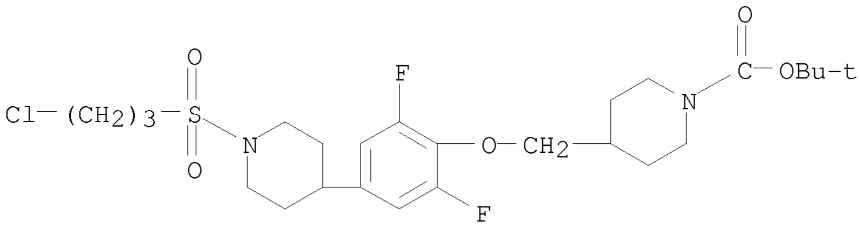
RN 1134109-65-1 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[2,6-difluoro-4-[1-[(3-hydroxypropyl)sulfonyl]-4-piperidinyl]phenoxy]methyl]-, 1-methylcyclopropyl ester (CA INDEX NAME)



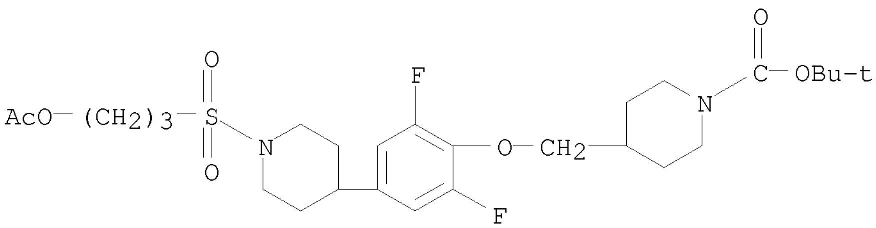
RN 1134110-07-8 CAPLUS
CN 4-Piperidinecarboxylic acid, 4-[4-[[1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl]methoxy]phenyl]-1-(methylsulfonyl)- (CA INDEX NAME)



IT 1134112-60-9P 1134112-62-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrazinylpiperazinyl sulfones as GPR119 modulators useful in treatment and prevention of GPR119 mediated diseases)
RN 1134112-60-9 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[4-[1-[(3-chloropropyl)sulfonyl]-4-piperidinyl]-2,6-difluorophenoxy]methyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)



RN 1134112-62-1 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[4-[1-[[3-(acetyloxy)propyl]sulfonyl]-4-piperidinyl]-2,6-difluorophenoxy]methyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:773795 CAPLUS
DOCUMENT NUMBER: 149:104606
TITLE: Piperidine-nitro derivatives as nonpeptidic renin inhibitors, their pharmaceutical compositions and use in the treatment of diseases
INVENTOR(S): Almirante, Nicoletta; Biondi, Stefano; Ongini, Ennio
PATENT ASSIGNEE(S): Nicox S.A., Fr.
SOURCE: PCT Int. Appl., 218pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

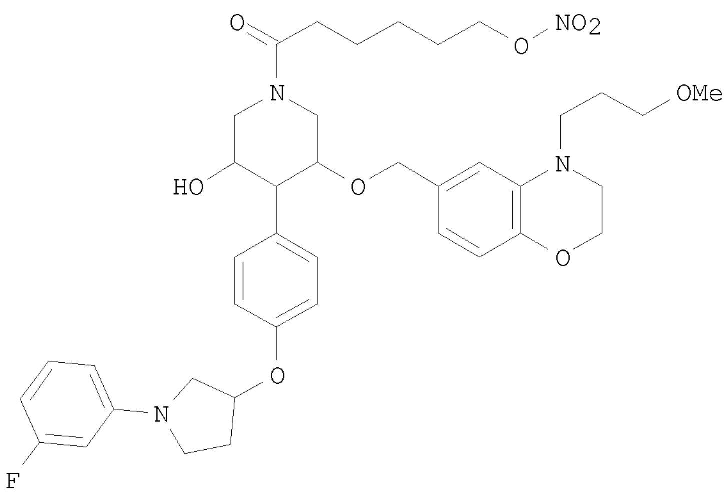
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008074450	A2	20080626	WO 2007-EP11078	20071213
WO 2008074450	A3	20090108		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,

BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
PRIORITY APPLN. INFO.: US 2006-875816P P 20061220
OTHER SOURCE(S): MARPAT 149:104606
GI

$A^1-(X?-ONO_2)_j$ I



II

AB Nonpeptidic renin inhibitors nitro derivs. of general formula I: having wider pharmacol. activity and enhanced tolerability. They can be employed for treating or preventing cardiovascular, renal and chronic liver diseases, inflammatory processes and metabolic syndrome. Compds. of formula I wherein A1 is substituted (mono/bi)azacycle; j is 1, 2, and 3; Xa is (un)branched CO-C1-20 alkylene, (un)branched CO2-C1-20 alkylene, CO-(CH2)0-20-aryl-(CH2)1-20, CO2-(CH2)0-20-aryl-(CH2)1-20, etc.; and their pharmaceutically acceptable salts, and stereoisomers thereof, are claimed. Compound II may be prepared by a general procedure. The compds. of the invention may be used as nonpeptidic renin inhibitors.

IT 1034701-37-5P 1034701-40-0P 1034701-41-1P
1034701-43-3P 1034701-44-4P 1034701-45-5P
1034701-46-6P 1034701-48-8P 1034701-49-9P
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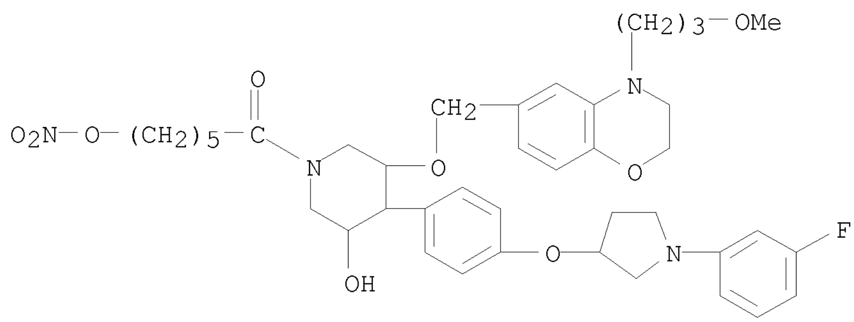
1034702-07-2P 1034702-08-3P 1034702-09-4P
1034702-10-7P 1034702-11-8P 1034702-12-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)
(drug candidate; preparation of piperidine-nitro derivs. of nonpeptidic renin inhibitors and their use in treating cardiovascular, renal, and liver diseases, inflammation, and metabolic syndrome)

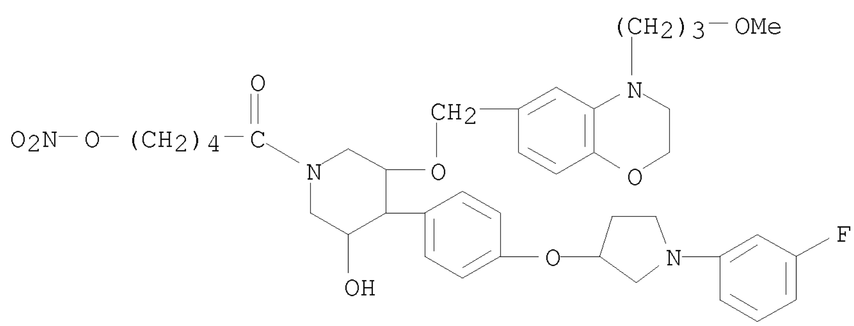
RN 1034701-37-5 CAPLUS

CN 1-Hexanone, 1-[3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-1-piperidinyl]-6-(nitrooxy)- (CA INDEX NAME)



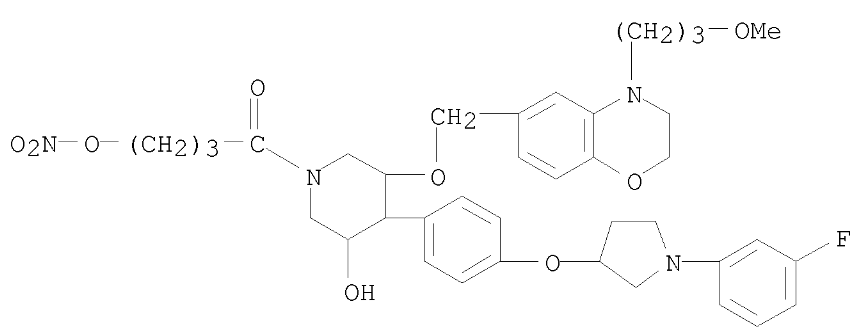
RN 1034701-40-0 CAPLUS

CN 1-Pentanone, 1-[3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-1-piperidinyl]-5-(nitrooxy)- (CA INDEX NAME)

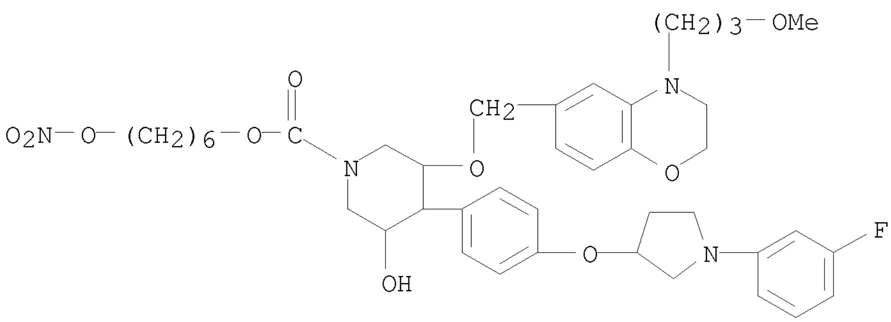


RN 1034701-41-1 CAPLUS

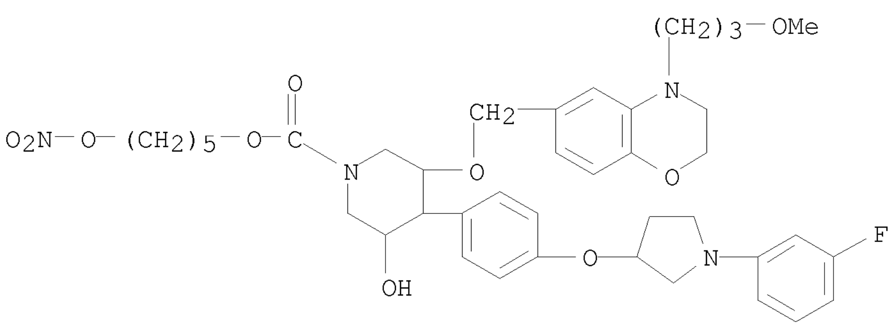
CN 1-Butanone, 1-[3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-1-piperidinyl]-4-(nitrooxy)- (CA INDEX NAME)



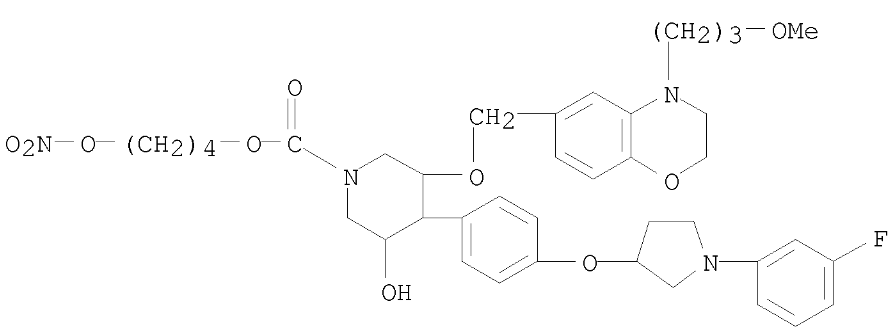
RN 1034701-43-3 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, 6-(nitrooxy)hexyl ester (CA INDEX NAME)



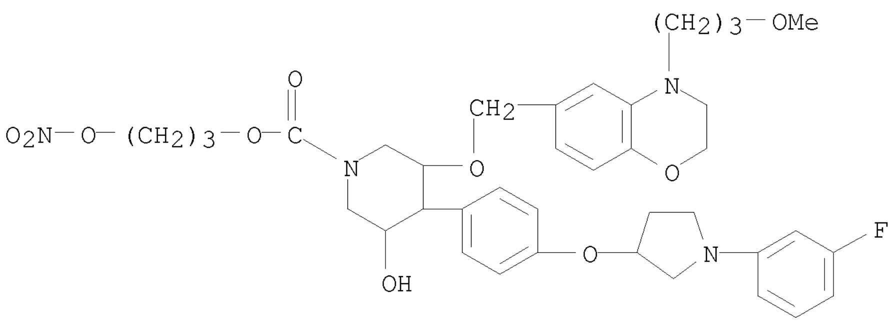
RN 1034701-44-4 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, 5-(nitrooxy)pentyl ester (CA INDEX NAME)



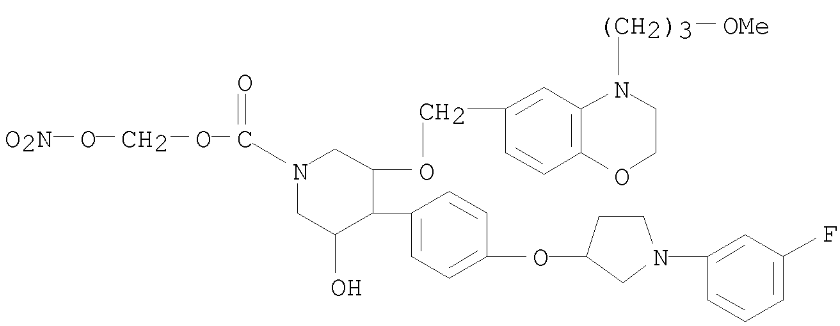
RN 1034701-45-5 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, 4-(nitrooxy)butyl ester (CA INDEX NAME)



RN 1034701-46-6 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, 3-(nitrooxy)propyl ester (CA INDEX NAME)

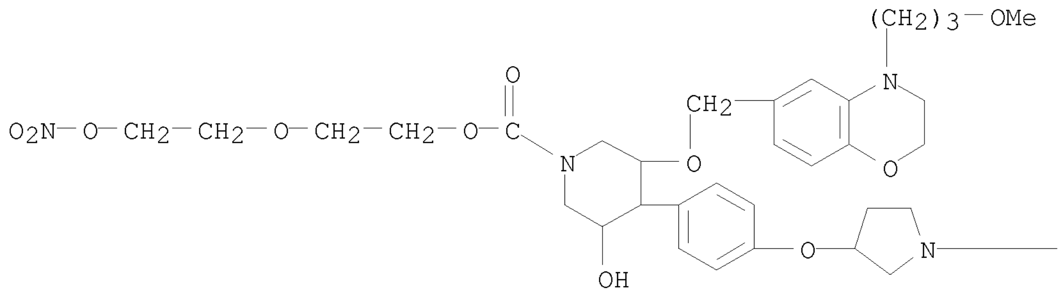


RN 1034701-48-8 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, (nitrooxy)methyl ester (CA INDEX NAME)

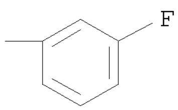


RN 1034701-49-9 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, 2-[2-(nitrooxy)ethoxy]ethyl ester (CA INDEX NAME)

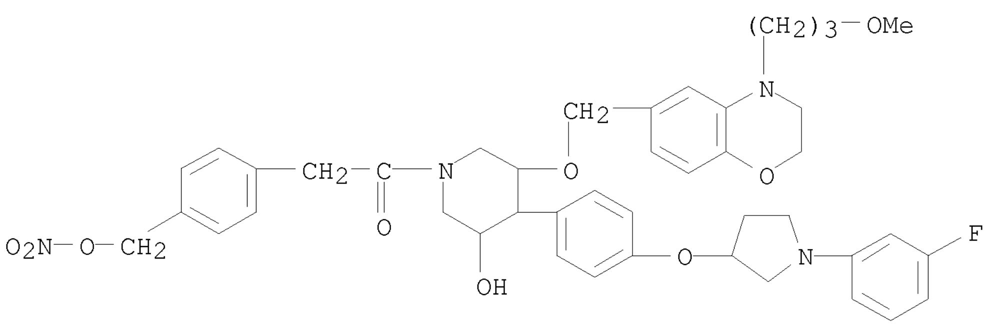
PAGE 1-A



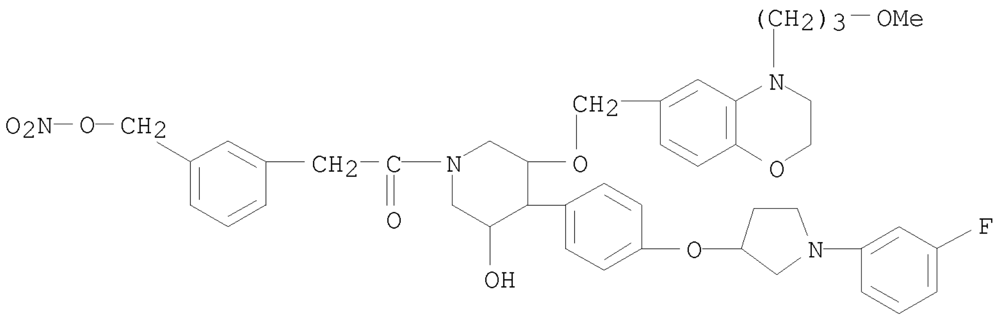
PAGE 1-B



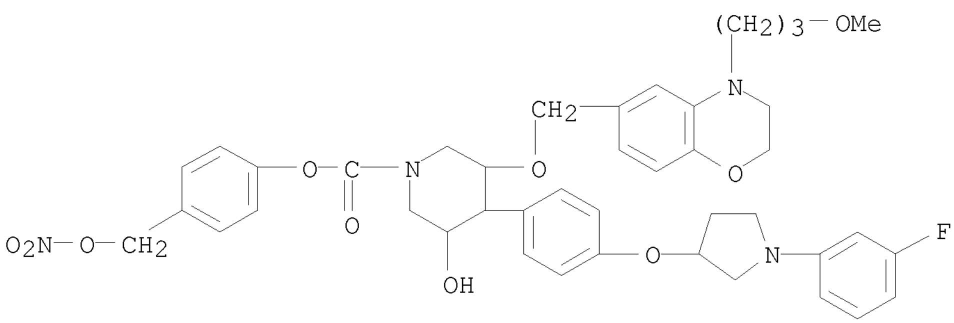
RN 1034701-52-4 CAPLUS
CN Ethanone, 1-[3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-1-piperidinyl]-2-[4-[(nitrooxy)methyl]phenyl]- (CA INDEX NAME)



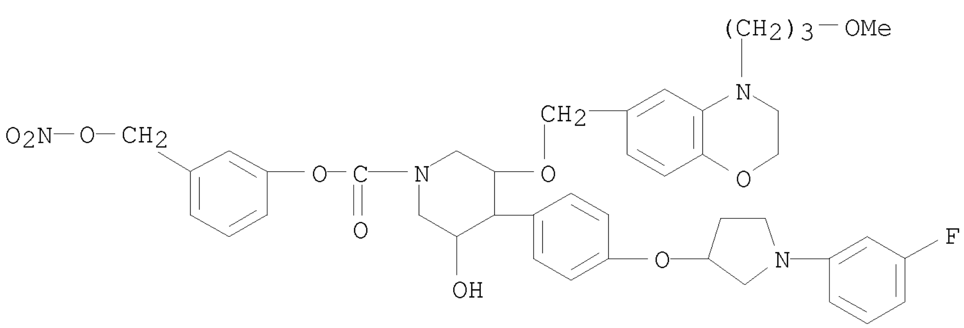
RN 1034701-53-5 CAPLUS
CN Ethanone, 1-[3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-1-piperidinyl]-2-[3-[(nitrooxy)methyl]phenyl]- (CA INDEX NAME)



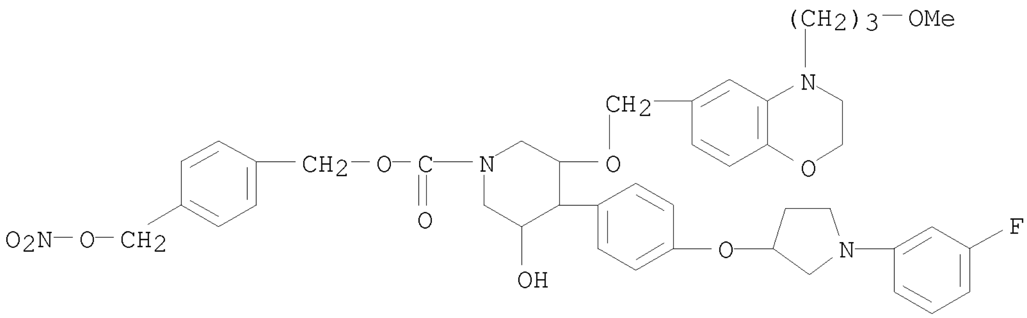
RN 1034701-55-7 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, 4-[(nitrooxy)methyl]phenyl ester (CA INDEX NAME)



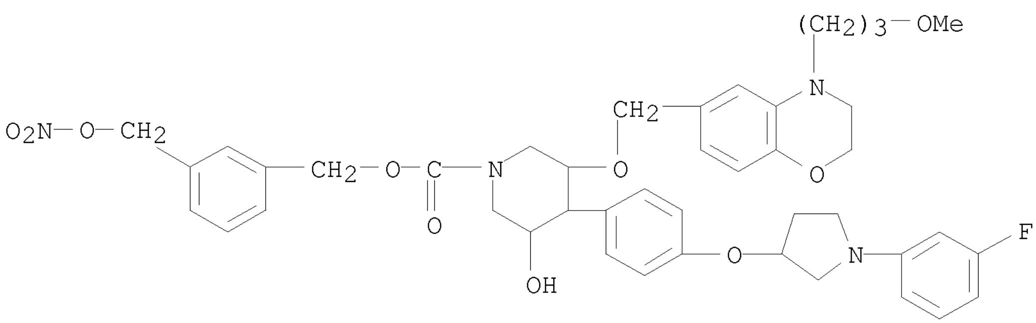
RN 1034701-57-9 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, 3-[(nitrooxy)methyl]phenyl ester (CA INDEX NAME)



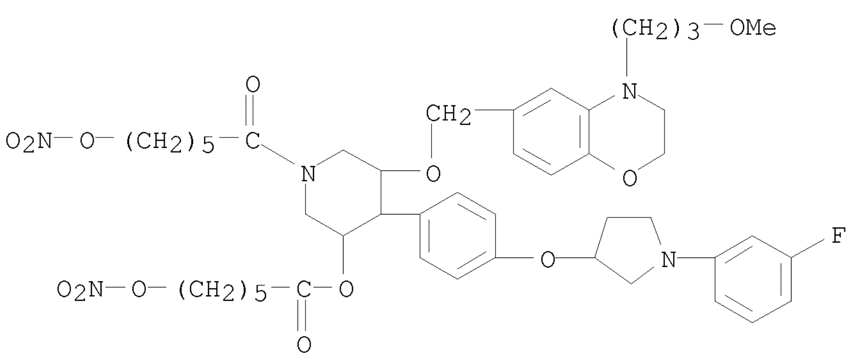
RN 1034701-58-0 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, [4-[(nitrooxy)methyl]phenyl]methyl ester (CA INDEX NAME)



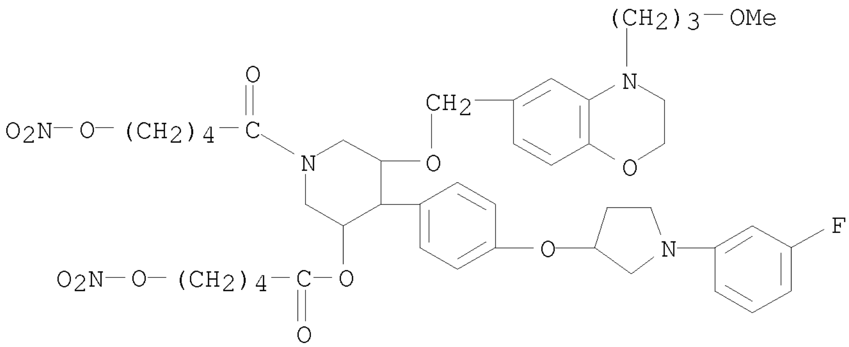
RN 1034701-59-1 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, [3-[(nitrooxy)methyl]phenyl]methyl ester (CA INDEX NAME)



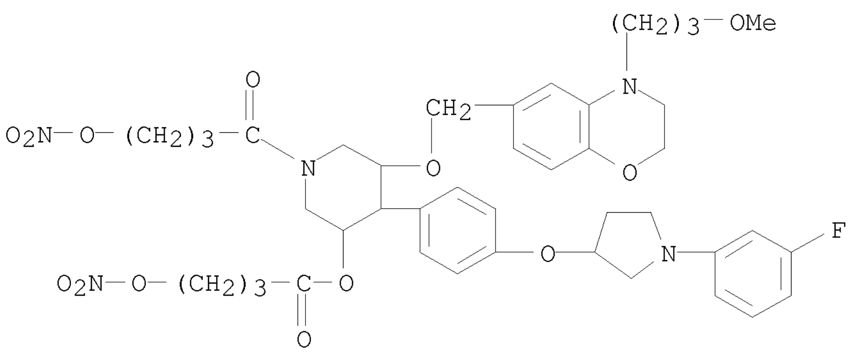
RN 1034701-61-5 CAPLUS
CN Hexanoic acid, 6-(nitrooxy)-, 5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-1-[6-(nitrooxy)-1-oxohexyl]-3-piperidinyl ester (CA INDEX NAME)



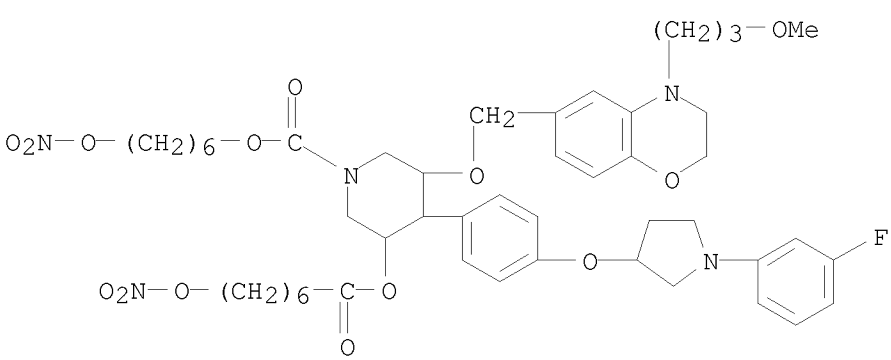
RN 1034701-63-7 CAPLUS
CN Pentanoic acid, 5-(nitrooxy)-, 5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-1-[5-(nitrooxy)-1-oxopentyl]-3-piperidinyl ester (CA INDEX NAME)



RN 1034701-64-8 CAPLUS
CN Butanoic acid, 4-(nitrooxy)-, 5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-1-[4-(nitrooxy)-1-oxobutyl]-3-piperidinyl ester (CA INDEX NAME)



RN 1034701-65-9 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[7-(nitrooxy)-1-oxoheptyl]oxy]-, 6-(nitrooxy)hexyl ester (CA INDEX NAME)



RN 1034701-66-0 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-

benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-
pyrrolidinyl]oxy]phenyl]-5-[[[[5-(nitrooxy)pentyl]oxy]carbonyl]oxy]-,
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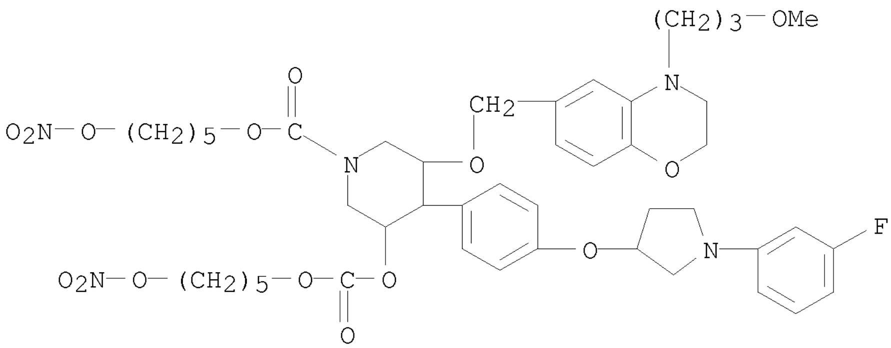
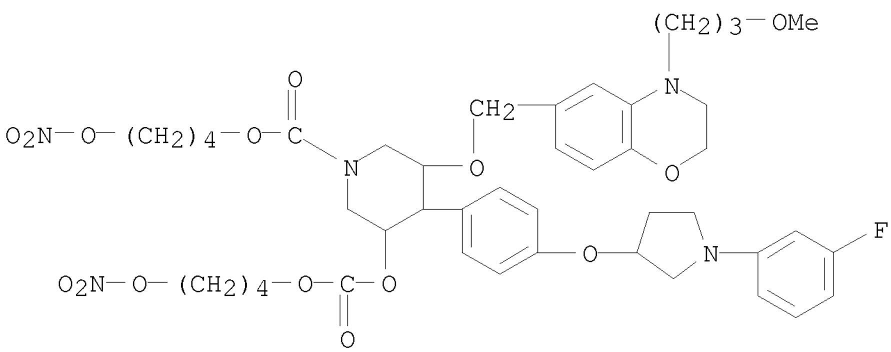
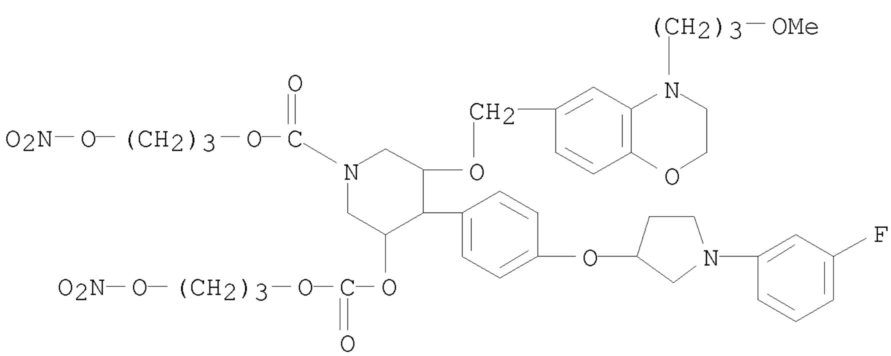


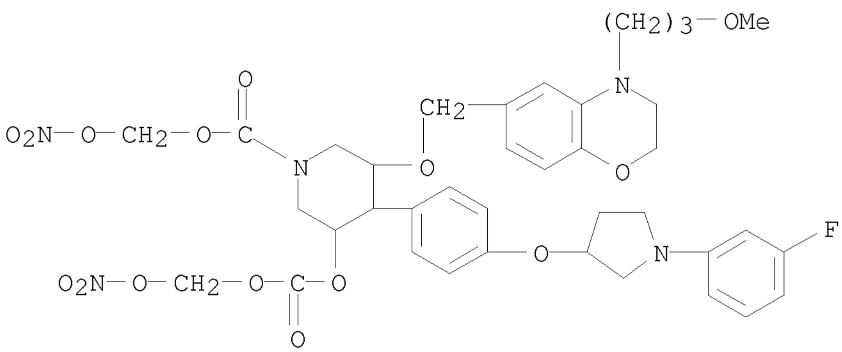
RN 1034701-67-1 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-
benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-
pyrrolidinyl]oxy]phenyl]-5-[[[4-(nitrooxy)butoxy]carbonyl]oxy]-,
4-(nitrooxy)butyl ester (CA INDEX NAME)



RN 1034701-68-2 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-
benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-
pyrrolidinyl]oxy]phenyl]-5-[[[3-(nitrooxy)propoxy]carbonyl]oxy]-,
3-(nitrooxy)propyl ester (CA INDEX NAME)

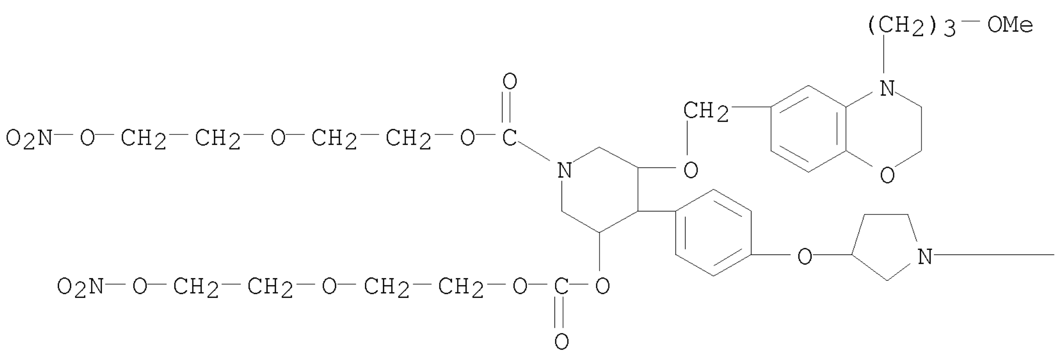


RN 1034701-69-3 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[[(nitrooxy)methoxy]carbonyl]oxy]-, (nitrooxy)methyl ester (CA INDEX NAME)



RN 1034701-70-6 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[[2-[2-(nitrooxy)ethoxy]ethoxy]carbonyl]oxy]-, 2-[2-(nitrooxy)ethoxy]ethyl ester (CA INDEX NAME)

PAGE 1-A



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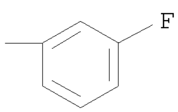
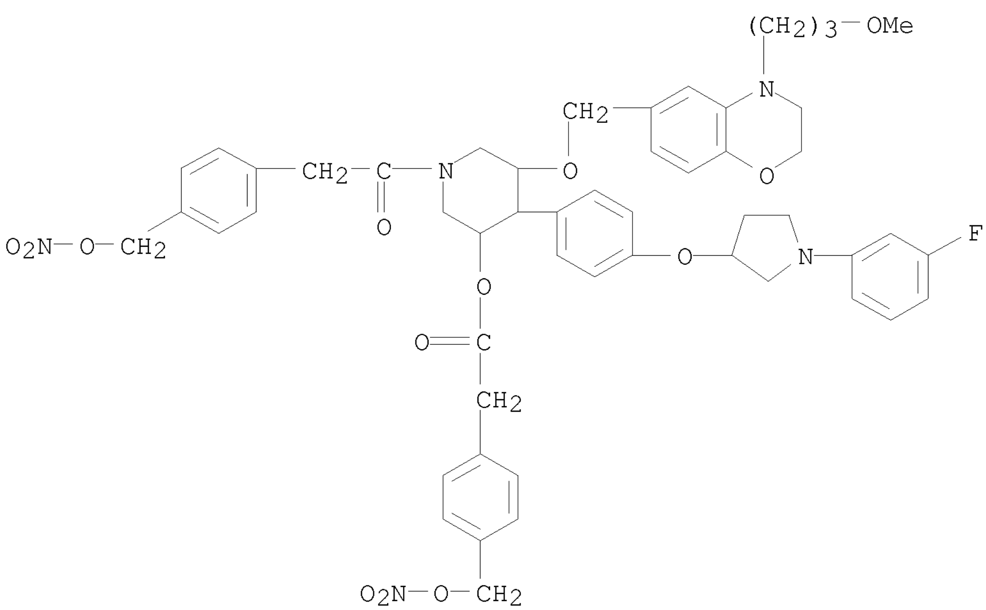
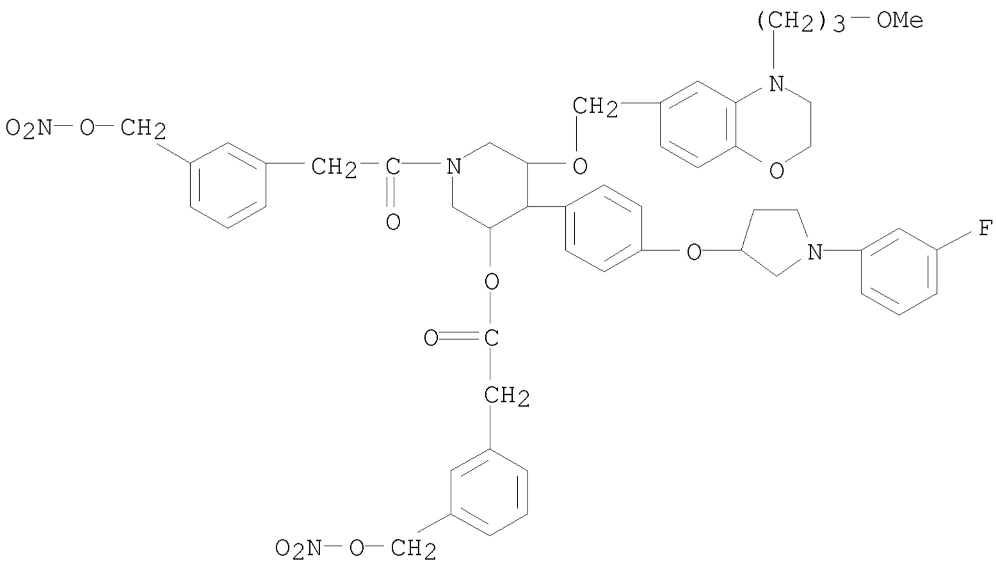


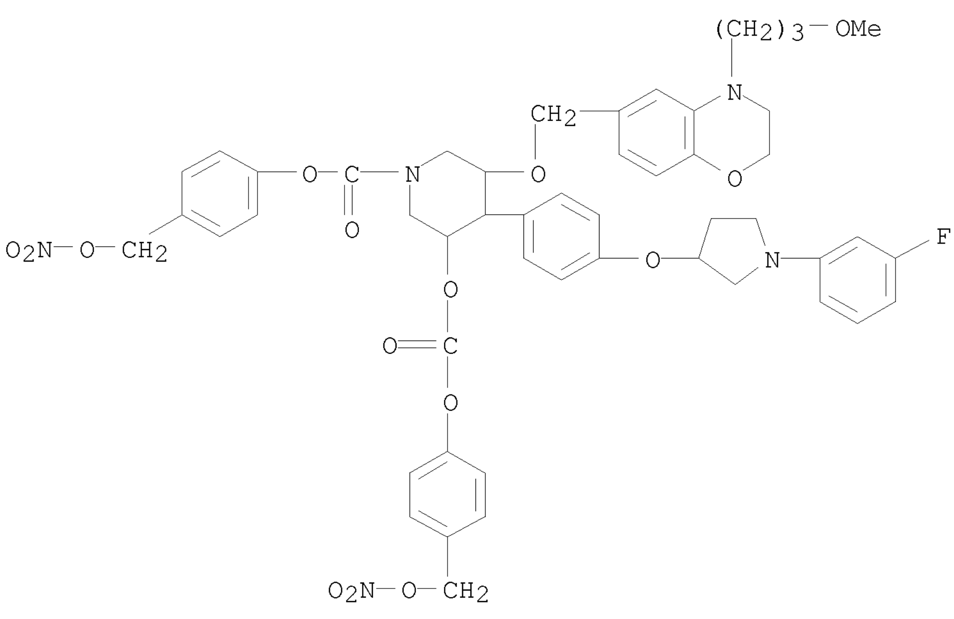
RN 1034701-73-9 CAPLUS
CN Benzeneacetic acid, 4-[(nitrooxy)methyl]-, 5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-1-[2-[4-[(nitrooxy)methyl]phenyl]acetyl]-3-piperidinyl ester (CA INDEX NAME)



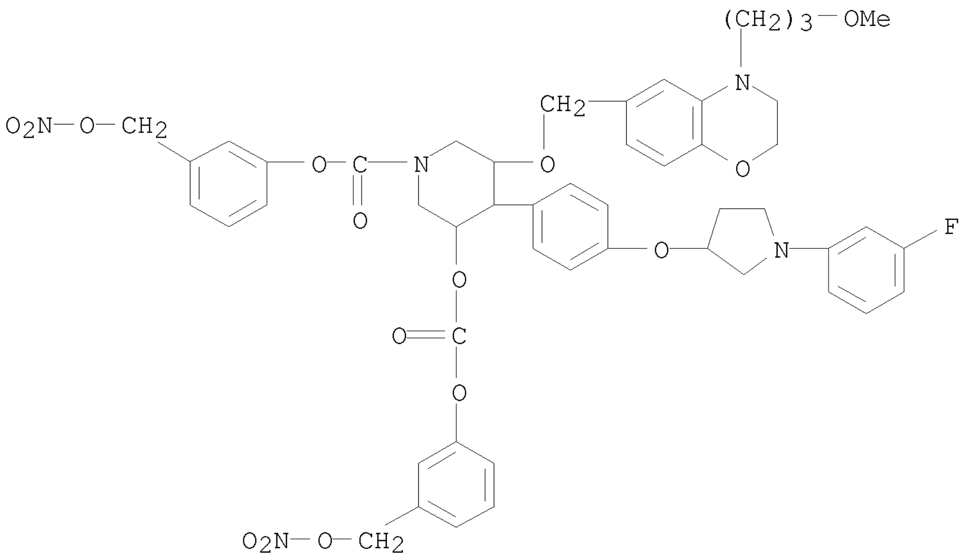
RN 1034701-74-0 CAPLUS
CN Benzeneacetic acid, 3-[(nitrooxy)methyl]-, 5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-1-[2-[3-[(nitrooxy)methyl]phenyl]acetyl]-3-piperidinyl ester (CA INDEX NAME)



RN 1034701-75-1 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[[4-[(nitrooxy)methyl]phenoxy]carbonyl]oxy]-, 4-[(nitrooxy)methyl]phenyl ester (CA INDEX NAME)



RN 1034701-76-2 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[[3-[(nitrooxy)methyl]phenoxy]carbonyl]oxy]-, 3-[(nitrooxy)methyl]phenyl ester (CA INDEX NAME)



RN 1034701-77-3 CAPLUS

CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[[[4-[(nitrooxy)methyl]phenyl]methoxy]carbonyl]oxy]-, [4-[(nitrooxy)methyl]phenyl]methyl ester (CA INDEX NAME)

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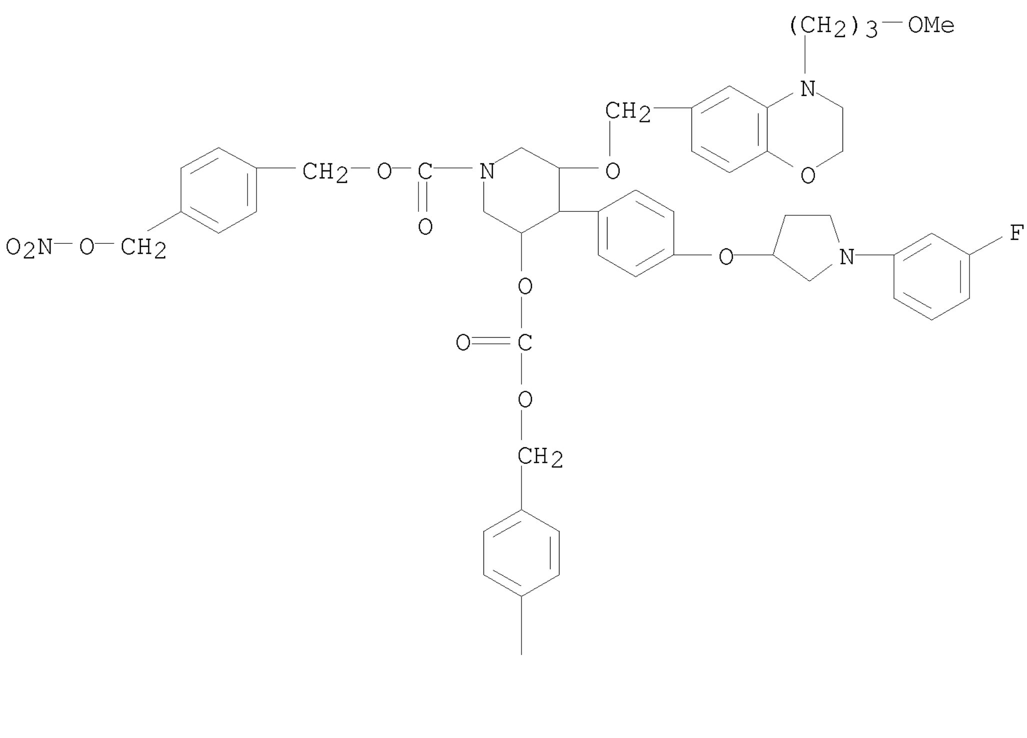
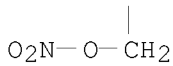
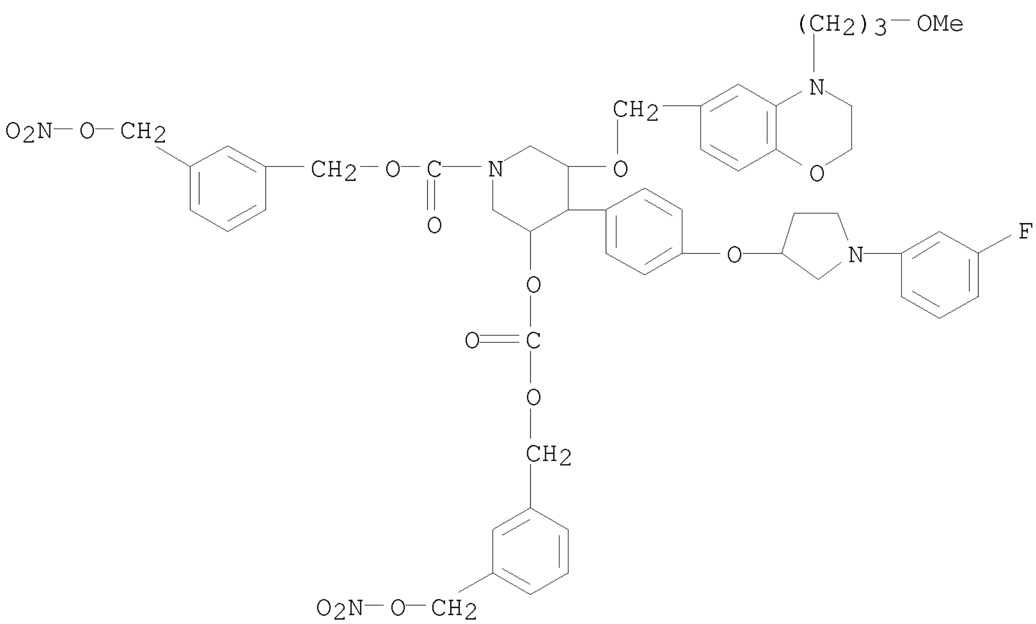


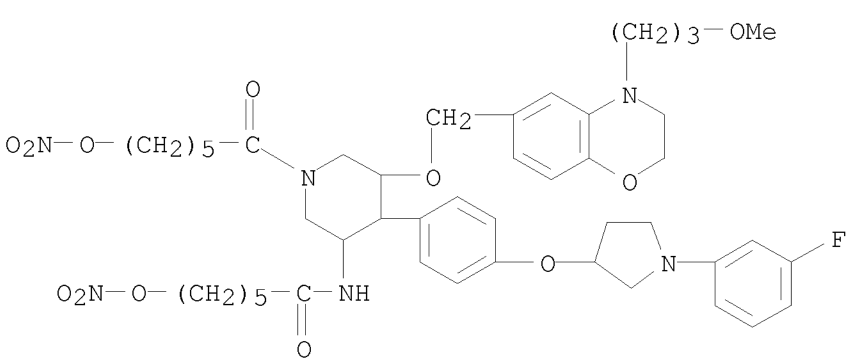
PAGE 2-A



RN 1034701-78-4 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[[[3-[(nitrooxy)methyl]phenyl]methoxy]carbonyl]oxy]-, [3-[(nitrooxy)methyl]phenyl]methyl ester (CA INDEX NAME)

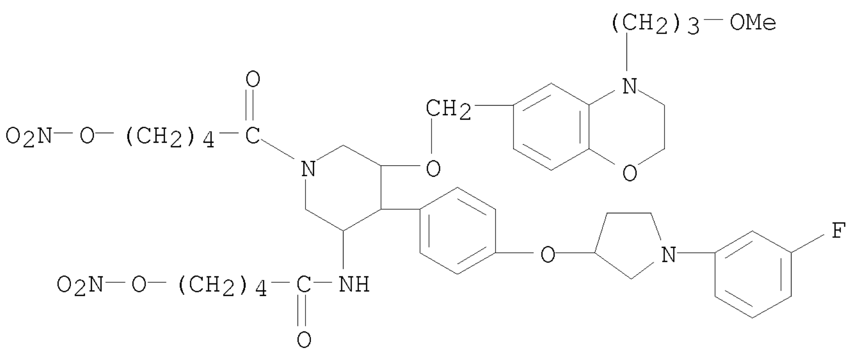


RN 1034701-96-6 CAPLUS
CN Hexanamide, N-[5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-1-[6-(nitrooxy)-1-oxohexyl]-3-piperidinyl]-6-(nitrooxy)- (CA INDEX NAME)



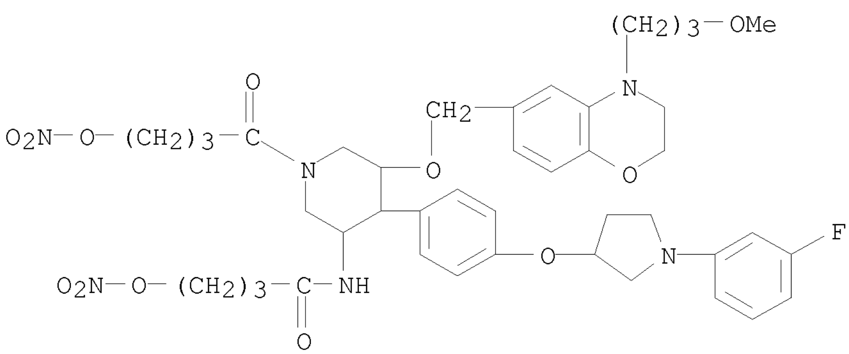
RN 1034701-97-7 CAPLUS
CN Pentanamide, N-[5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-

yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-1-[5-(nitrooxy)-1-oxopentyl]-3-piperidinyl]-5-(nitrooxy)- (CA INDEX NAME)



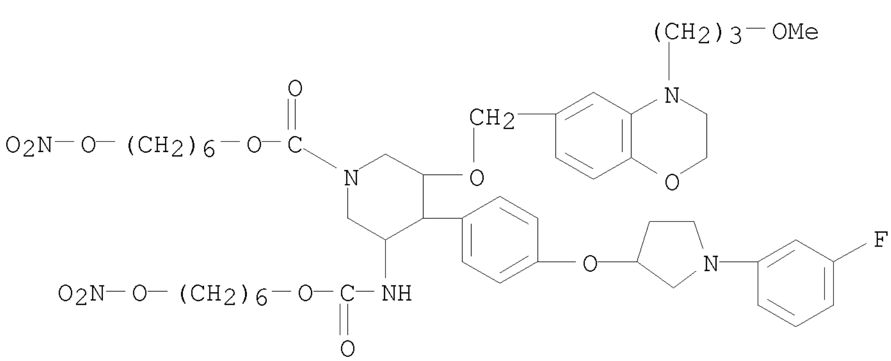
RN 1034701-98-8 CAPLUS

CN Butanamide, N-[5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-1-[4-(nitrooxy)-1-oxobutyl]-3-piperidinyl]-4-(nitrooxy)- (CA INDEX NAME)



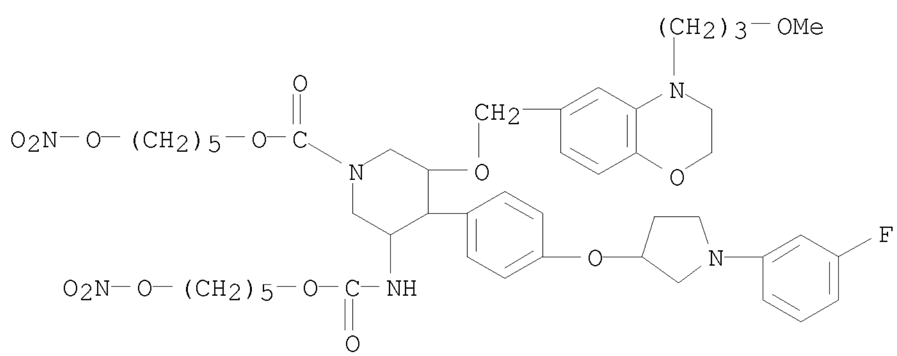
RN 1034701-99-9 CAPLUS

CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[[[6-(nitrooxy)hexyl]oxy]carbonyl]amino]-, 6-(nitrooxy)hexyl ester (CA INDEX NAME)



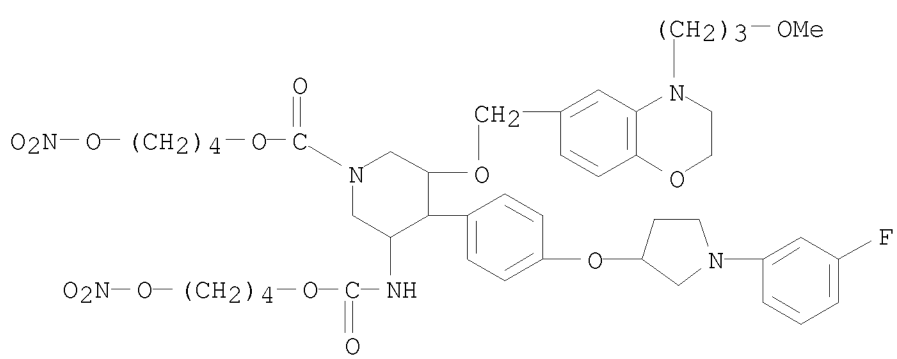
RN 1034702-00-5 CAPLUS

CN   1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-
     benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-
     pyrrolidinyl]oxy]phenyl]-5-[[[[5-(nitrooxy)pentyl]oxy]carbonyl]amino]-,
     5-(nitrooxy)pentyl ester (CA INDEX NAME)



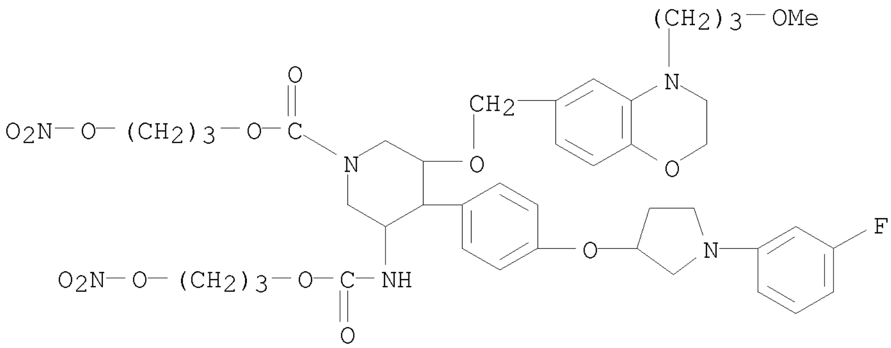
RN   1034702-01-6 CAPLUS

CN   1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-
     benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-
     pyrrolidinyl]oxy]phenyl]-5-[[[4-(nitrooxy)butoxy]carbonyl]amino]-,
     4-(nitrooxy)butyl ester (CA INDEX NAME)

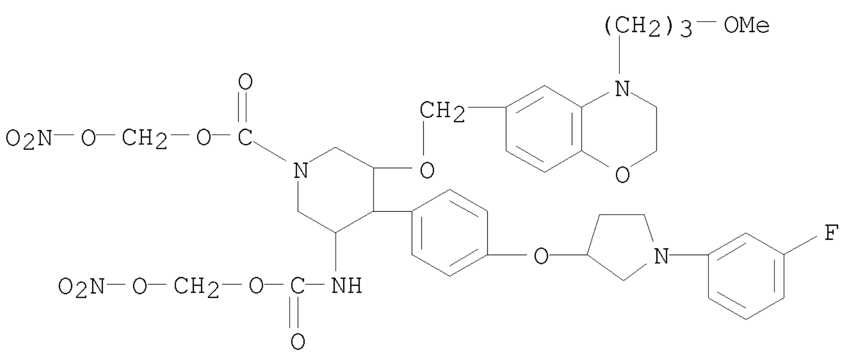


RN   1034702-02-7 CAPLUS

CN   1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-
     benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-
     pyrrolidinyl]oxy]phenyl]-5-[[[3-(nitrooxy)propoxy]carbonyl]amino]-,
     3-(nitrooxy)propyl ester (CA INDEX NAME)



RN 1034702-03-8 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[[(nitrooxy)methoxy]carbonyl]amino]-, (nitrooxy)methyl ester (CA INDEX NAME)



RN 1034702-04-9 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[[2-[2-(nitrooxy)ethoxy]ethoxy]carbonyl]amino]-, 2-[2-(nitrooxy)ethoxy]ethyl ester (CA INDEX NAME)

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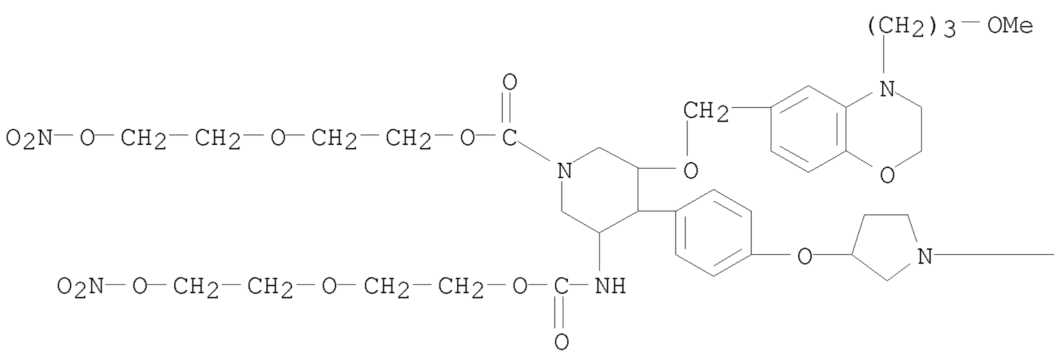
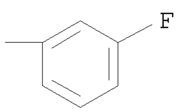
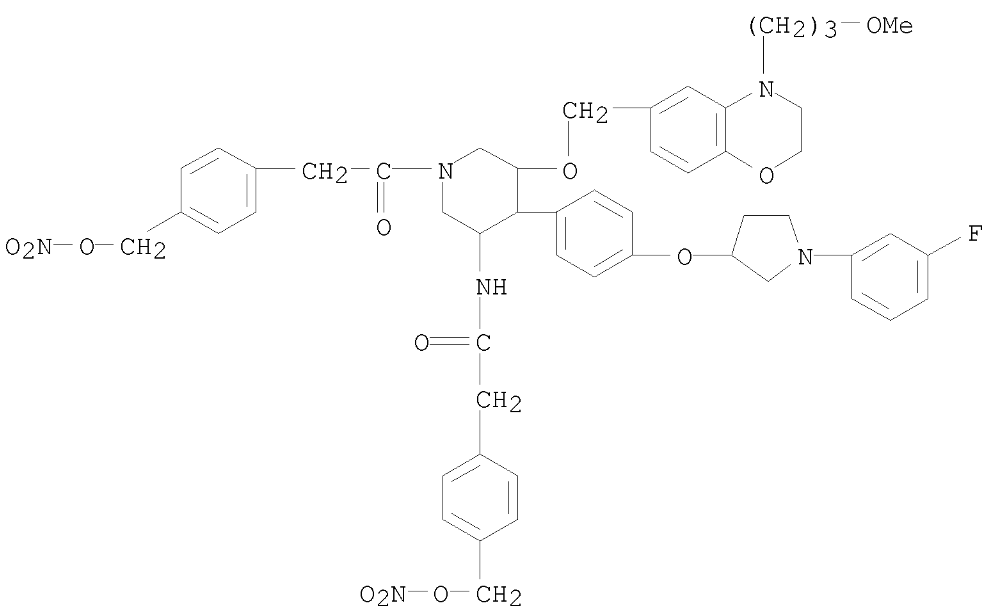


PAGE 1-B



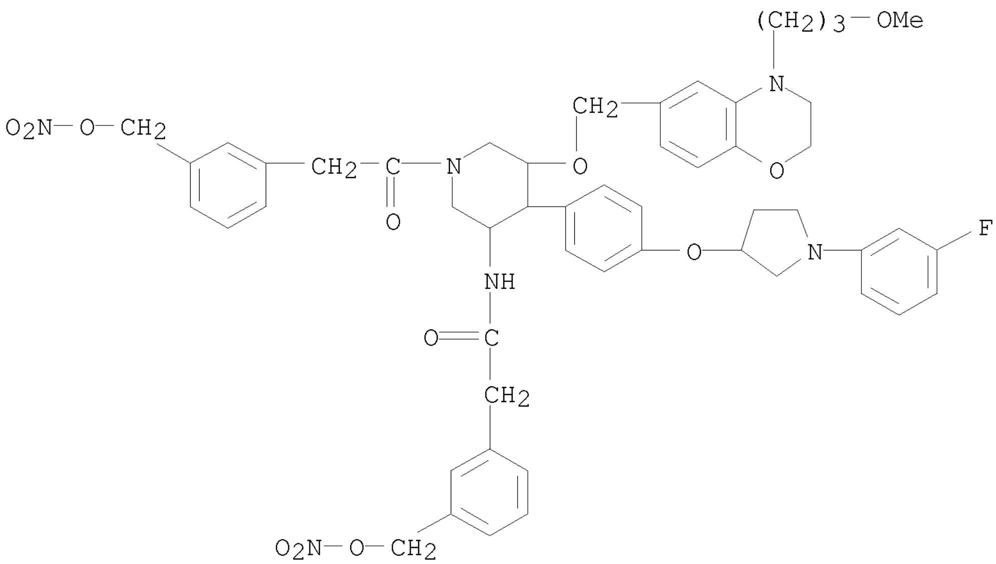
RN 1034702-07-2 CAPLUS

CN Benzeneacetamide, N-[5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-1-[2-[4-[(nitrooxy)methyl]phenyl]acetyl]-3-piperidinyl]-4-[(nitrooxy)methyl]- (CA INDEX NAME)

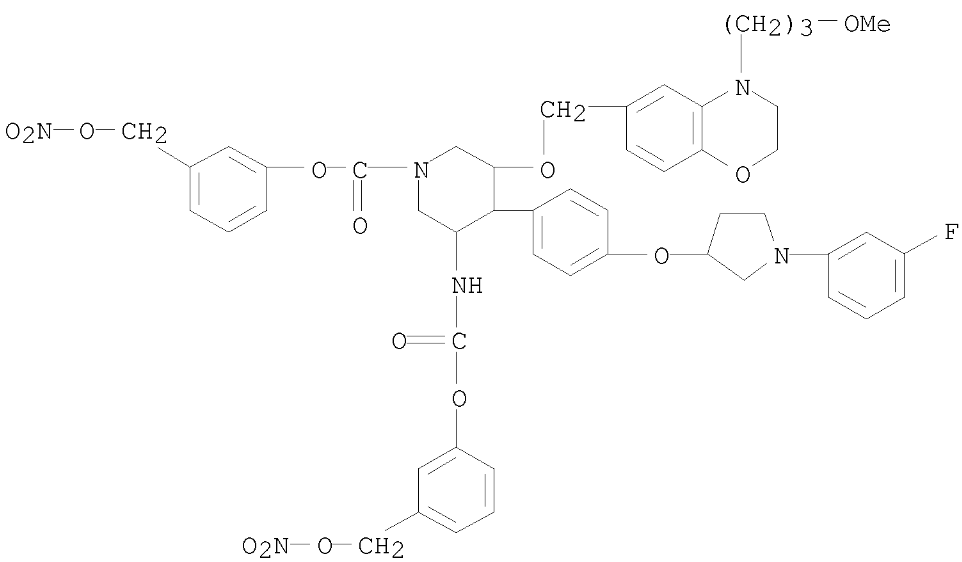


RN 1034702-08-3 CAPLUS

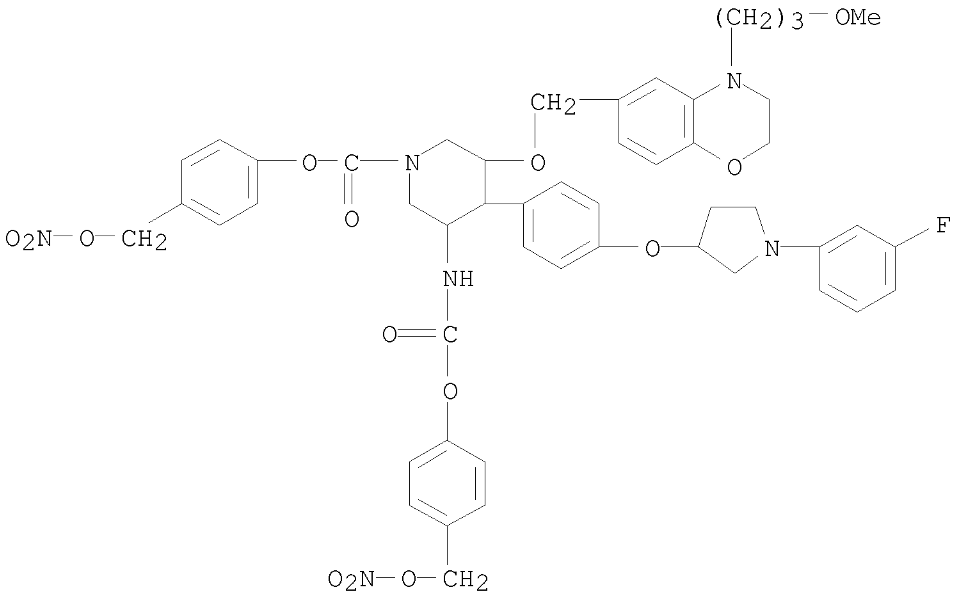
CN Benzeneacetamide, N-[5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-1-[2-[3-[(nitrooxy)methyl]phenyl]acetyl]-3-piperidinyl]-3-[(nitrooxy)methyl]- (CA INDEX NAME)



RN 1034702-09-4 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[[3-[(nitrooxy)methyl]phenoxy]carbonyl]amino]-, 3-[(nitrooxy)methyl]phenyl ester (CA INDEX NAME)



RN 1034702-10-7 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[[4-[(nitrooxy)methyl]phenoxy]carbonyl]amino]-, 4-[(nitrooxy)methyl]phenyl ester (CA INDEX NAME)



RN   1034702-11-8 CAPLUS
CN   1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[[[4-[(nitrooxy)methyl]phenyl]methoxy]carbonyl]amino]-, [4-[(nitrooxy)methyl]phenyl]methyl ester (CA INDEX NAME)

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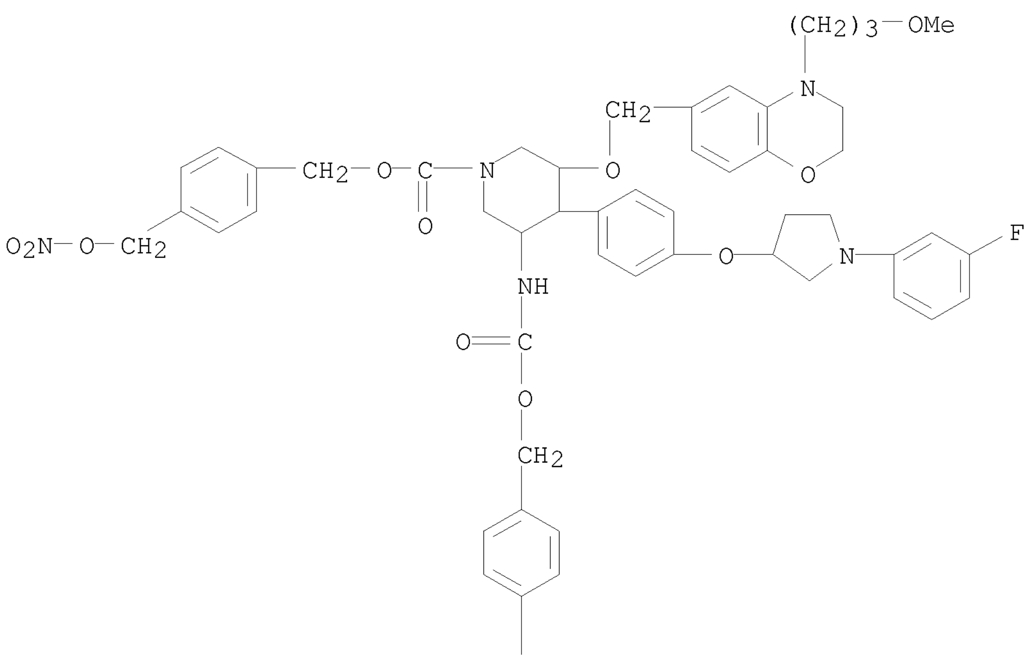

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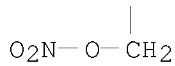
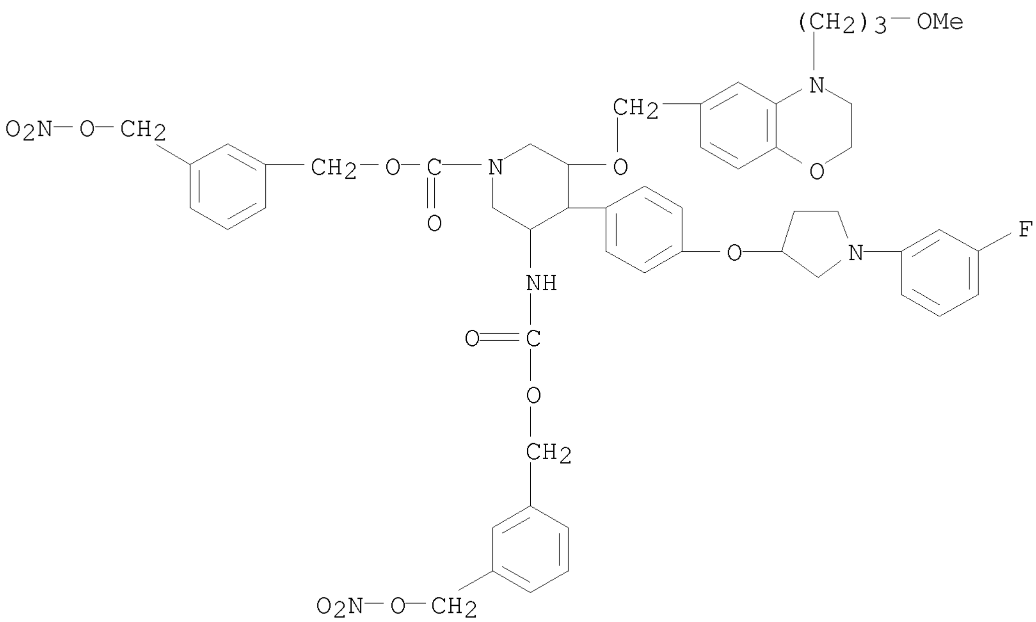


RN 1034702-12-9 CAPLUS

CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[[[3-[(nitrooxy)methyl]phenyl]methoxy]carbonyl]amino]-, [3-[(nitrooxy)methyl]phenyl]methyl ester (CA INDEX NAME)

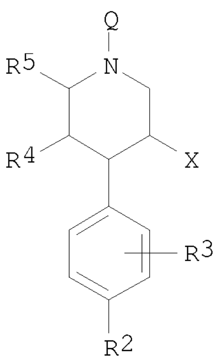


L4 ANSWER 3 OF 10 CAPLUS

ACCESSION NUMBER: 2008:436471 CAPLUS
DOCUMENT NUMBER: 148:449461
TITLE: Arylpiperidine derivatives as renin inhibitors
PATENT ASSIGNEE(S): Speedel Experimenta AG, Switz.
SOURCE: Eur. Pat. Appl., 72pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1908761	A1	20080409	EP 2006-121769	20061004
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
EP 1908762	A2	20080409	EP 2007-117831	20071003
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR,				

AL, BA, HR, MK, RS
PRIORITY APPLN. INFO.: EP 2006-121769 A 20061004
OTHER SOURCE(S): MARPAT 148:449461
GI



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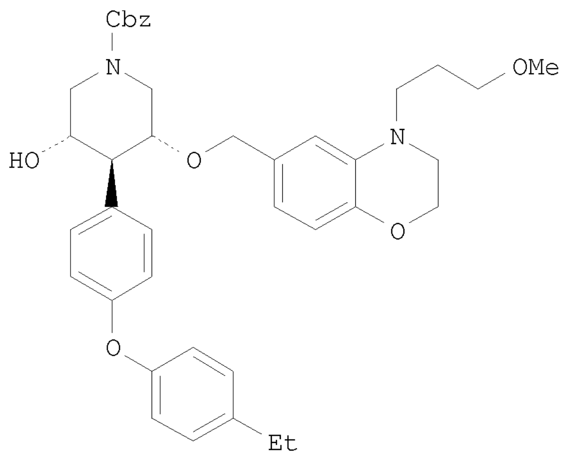


II

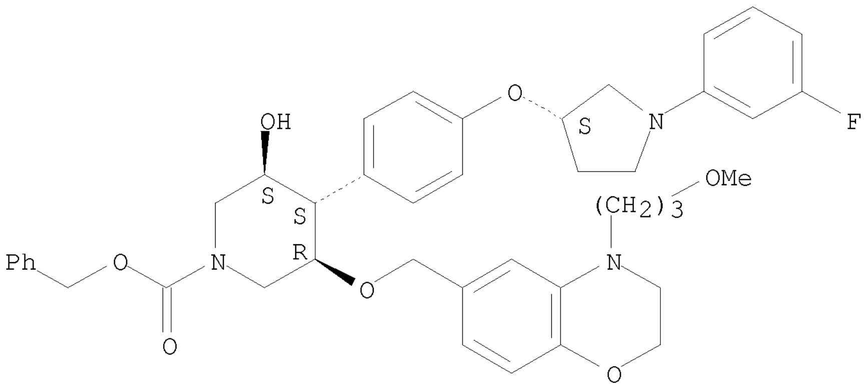
AB Title compds. I [R2 = alkenyloxy, alkoxy, alkoxyalkoxy, etc.; R3 = H or halo (one or two halo substituents possible); R4 = H or when R5 = H, R4 = (un)substituted alkoxy, alkoxyalkoxy, cyanoalkoxy, etc.; R5 = H or when R4 = H, R5 = alkenyl, alkyl, alkylsulfonylalkyl, etc.; X = R1O-alkyl, R1-alkylthio, R1-alkyl, etc.; R1 = aryl or heterocyclyl; Q = H or CO2CHR7OC(O)R8; R7 = (un)substituted alkyl or arylalkyl; R8 = alkyl], and their pharmaceutically acceptable salts, are prepared and disclosed as renin inhibitors. Intermediate II was prepared by coupling of (3R,4R,5S)-4-(4-hydroxyphenyl)-3-[4-(3-methoxypropyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethoxy]5-triisopropylsilanyloxypiperidine-1-carboxylic acid benzyl ester (preparation given) with 4-ethylphenylboronic acid followed by desilylation. Methods for converting intermediate II to a compound of formula I are described which involve esterification and deprotection. Assays for inhibiting PEPT1 transporter indicate I have inhibitory effects in the in vitro system at minimal concns. of about 10-2 to about 10-5 mol/L. Pharmacokinetic properties are also analyzed with compds. of the invention effectively increasing concentration of parent compound in plasma in the in vivo test described at doses of about 0.3 to about 30 mg/kg p.o. Moreover, the enzymic substrate portion of the compound is simultaneously a substrate for a membrane transporter.

IT 873945-20-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(Starting material; preparation of arylpiperidine derivs. as renin inhibitors)

RN 873945-20-1 CAPLUS

CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, phenylmethyl ester, (3R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

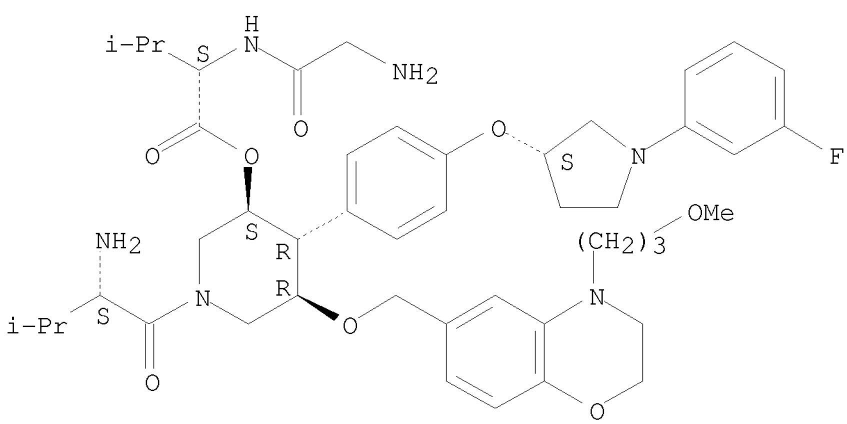


IT 1019261-38-1P 1019261-40-5P 1019261-42-7P
1019261-44-9P 1019261-46-1P 1019261-48-3P
1019261-50-7P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of arylpiperidine derivs. as renin inhibitors)

RN 1019261-38-1 CAPLUS

CN L-Valine, glycyl-, (3S,4R,5R)-1-[(2S)-2-amino-3-methyl-1-oxobutyl]-5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-3-piperidinyl ester (CA INDEX NAME)

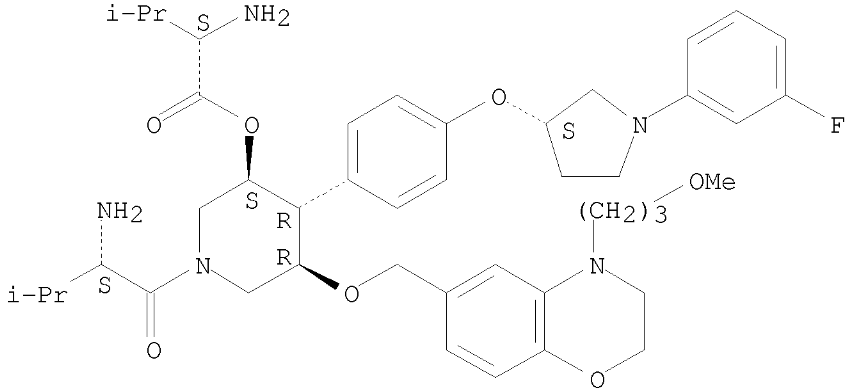
Absolute stereochemistry.



RN 1019261-40-5 CAPLUS

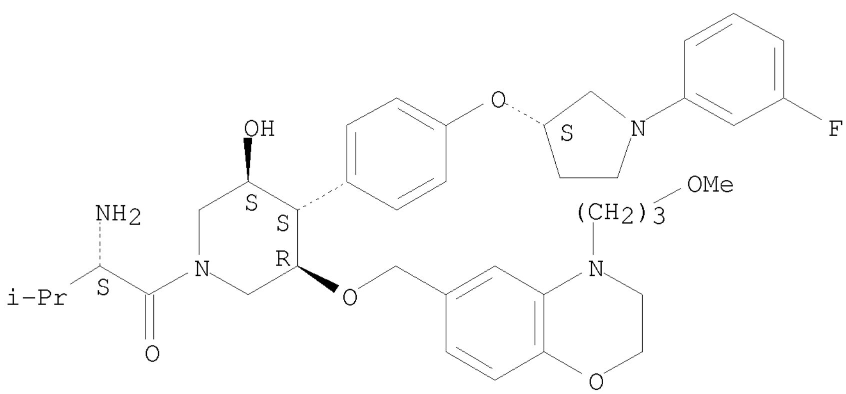
CN L-Valine, (3S,4R,5R)-1-[(2S)-2-amino-3-methyl-1-oxobutyl]-5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-3-piperidinyl ester (CA INDEX NAME)

Absolute stereochemistry.



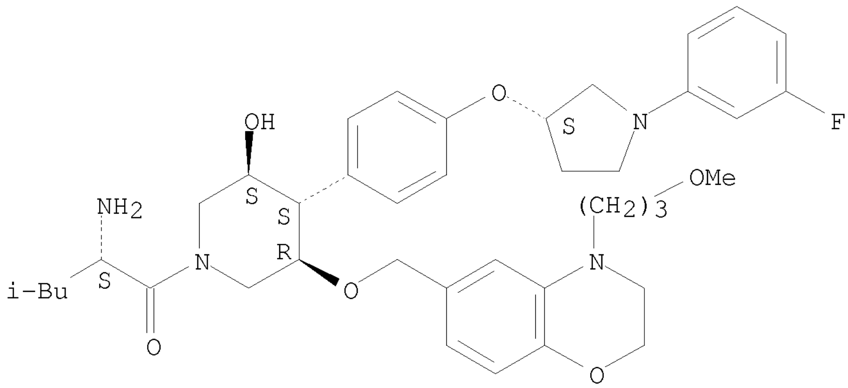
RN 1019261-42-7 CAPLUS
CN 1-Butanone, 2-amino-1-[(3R,4S,5S)-3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-1-piperidinyl]-3-methyl-, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



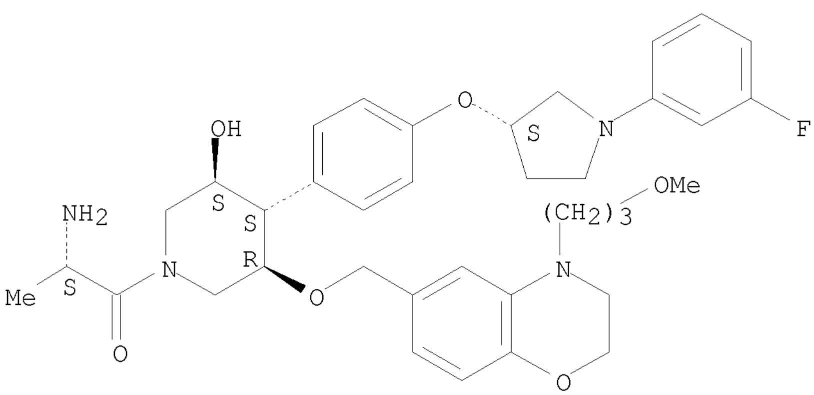
RN 1019261-44-9 CAPLUS
CN 1-Pentanone, 2-amino-1-[(3R,4S,5S)-3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-1-piperidinyl]-4-methyl-, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



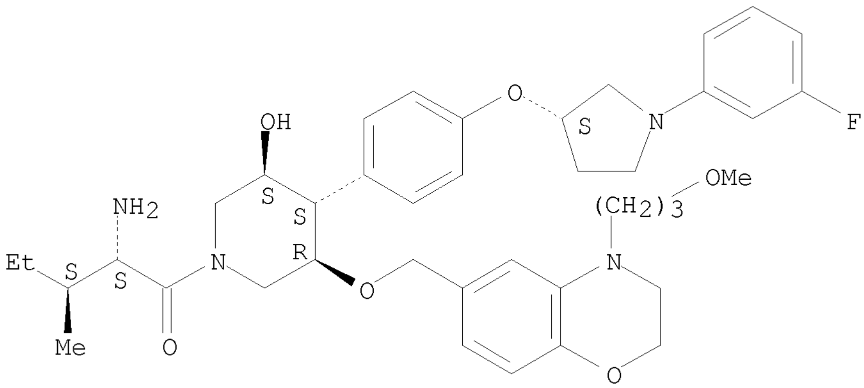
RN 1019261-46-1 CAPLUS
CN 1-Propanone, 2-amino-1-[(3R,4S,5S)-3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-1-piperidinyl]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



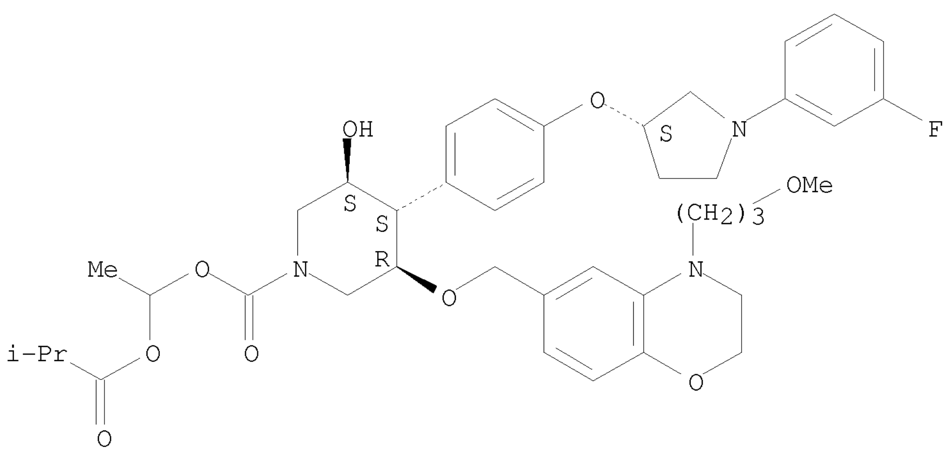
RN 1019261-48-3 CAPLUS
CN 1-Pentanone, 2-amino-1-[(3R,4S,5S)-3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-1-piperidinyl]-3-methyl-, (2S,3S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1019261-50-7 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, 1-(2-methyl-1-oxopropoxy)ethyl ester, (3R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:191818 CAPLUS
DOCUMENT NUMBER: 148:262597
TITLE: Nitrate esters of piperidines and their preparation, pharmaceutical compositions and use in the treatment of cardiovascular diseases
INVENTOR(S): Herold, Peter; Mah, Robert; Stutz, Stefan; Tschinke, Vincenzo; Lyothier, Isabelle; Schumacher, Christoph; Marti, Christiane; Jotterand, Nathalie
PATENT ASSIGNEE(S): Speedel Experimenta AG, Switz.
SOURCE: PCT Int. Appl., 113pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008017685	A1	20080214	WO 2007-EP58207	20070807
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2007283631	A1	20080214	AU 2007-283631	20070807
EP 2049514	A1	20090422	EP 2007-788301	20070807
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				

PRIORITY APPLN. INFO.: CH 2006-1279 A 20060808
WO 2007-EP58207 W 20070807
OTHER SOURCE(S): MARPAT 148:262597
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

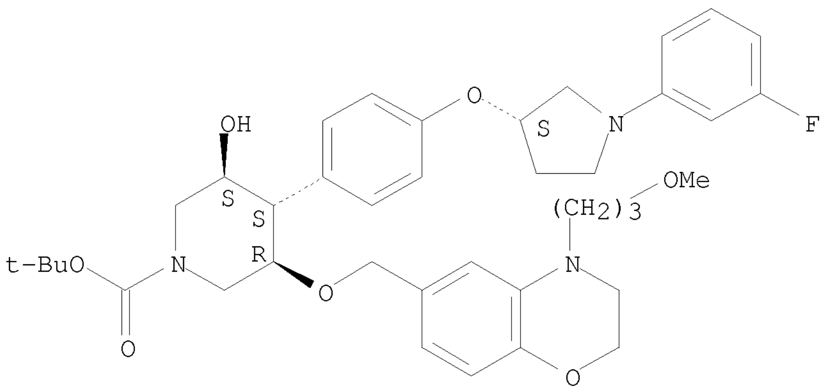
AB The application relates to novel nitrate ester derivs. of substituted piperidines of the general formula I, a process for their preparation and the use of these compds. as a curative agent in cardiovascular diseases, in particular in high blood pressure and vascular and organ damage accompanying high blood pressure. Compds. of formula I wherein R1 is aryl and heterocyclyl; R2 is C2-8 alkenyloxy-C1-8 alkoxy, C2-8 alkenyloxy-C1-8 alkyl, C1-8 alkoxy, etc.; R3 is halo; Y is (un)substituted C1-8 alkylene, (un)substituted C1-8 alkylenyloxy-C1-8 alkylene, C1-8 alkylcarbonyl-C1-8 alkylene, etc.; Z is (un)substituted C1-8 alkylene-CO2, (un)substituted C1-8 alkylene-OCO2, (un)substituted C1-8 alkylene-CO-NH-CO and derivs., etc.; m is 0, 1 and 2; n, p and q are independently 0 and 1, where p is 0, q is 1; and p is 1 where q is 0; and their salts and their pharmaceutically usable salts thereof, are claimed. Example compound II was prepared by a general procedure (procedure given). All the invention compds. were evaluated for their renin inhibitory activity.

IT 1006866-19-8P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prophetic intermediate; preparation of nitrate ester derivs. of substituted piperidines useful in treatment and prevention of cardiovascular diseases)

RN 1006866-19-8 CAPLUS

CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, 1,1-dimethylethyl ester, (3R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



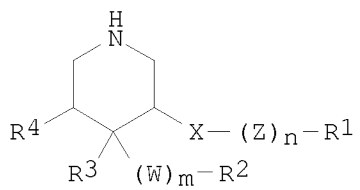
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:793715 CAPLUS
DOCUMENT NUMBER: 147:189075
TITLE: 3,4,5-Substituted piperidines as β-secretase, cathepsin D, plasmepsin II and HIV protease inhibitors and their preparation and use in the treatment of diseases
INVENTOR(S): Herold, Peter; Mah, Robert; Stutz, Stefan; Tschinke, Vincenzo; Schumacher, Christoph; Stojanovic, Aleksandar; Jotterand, Nathalie; Behnke, Dirk
PATENT ASSIGNEE(S): Switz.
SOURCE: U.S. Pat. Appl. Publ., 108pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

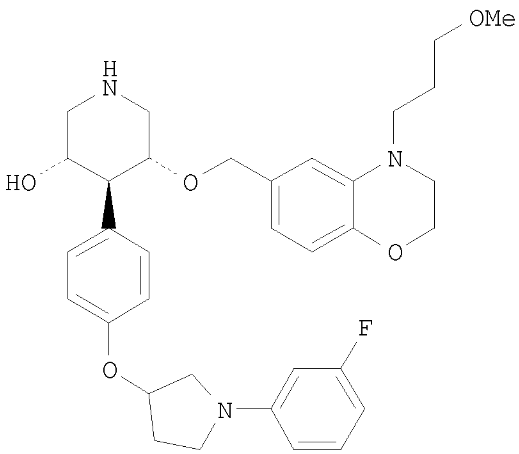
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070167433	A1	20070719	US 2007-655108	20070119
EP 1816122	A2	20070808	EP 2007-100713	20070118
EP 1816122	A3	20070919		

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU

PRIORITY APPLN. INFO.: CH 2006-88 A 20060119
OTHER SOURCE(S): MARPAT 147:189075
GI



I



II

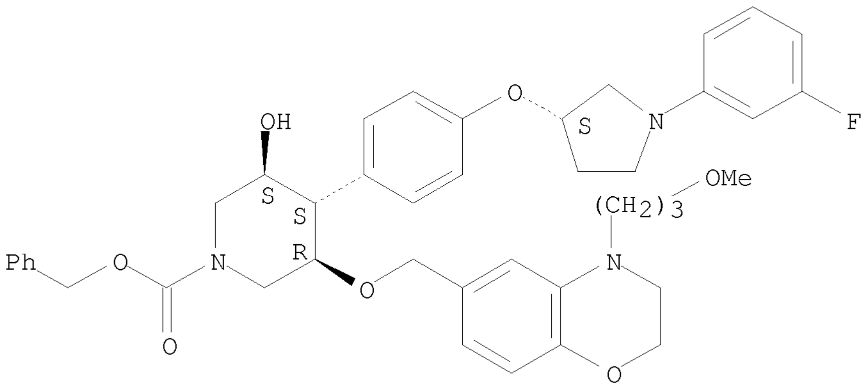
AB Use of compds. of the general formula I and pharmaceutically acceptable salt thereof, asβsecretase, cathepsin D, plasmepsin II and/or HIV protease inhibitors. Compds. of formula I wherein R1 is (un)substituted heterocyclyl and (un)substituted aryl; R2 is Ph, naphthyl, acenaphthyl, pyridinyl, pyrimidinyl, etc.; R3 is H, OH, C1-8 alkoxy, and C1-8 alkenyloxy; R4 is (un)substituted C1-8 alkyl, (un)substituted C1-8 alkoxy-C1-8 alkyl, (mono/di)-C1-8 alkylamino-C1-8 alkyl, etc.; X is a bond, O, S, (un)substituted methylene, CHOH and derivs., etc.; W is O and S; Z is (un)substituted C1-8 alkylene, C2-8 alkenylene, O, N, S, etc.; n is 1 or n is 0 and 1 when X is OCO; m is 0 and 1; and their pharmaceutically acceptable salts, prodrugs, and stable non-radioactive isotopes thereof, are claimed. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their β-secretase, cathepsin D, plasmepsin II and HIV protease inhibitory activity.

IT 873945-20-1P 873945-22-3P 873945-23-4P
873945-25-6P 873946-26-0P 873946-30-6P
873946-31-7P 873946-42-0P 873946-43-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of trisubstituted piperidines as β-secretase, cathepsin D, plasmepsin II and HIV-protease inhibitors useful in the treatment of diseases)

RN 873945-20-1 CAPLUS

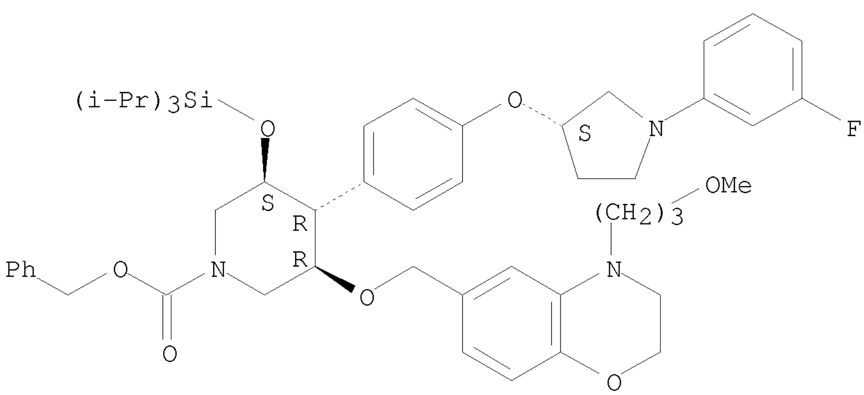
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, phenylmethyl ester, (3R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



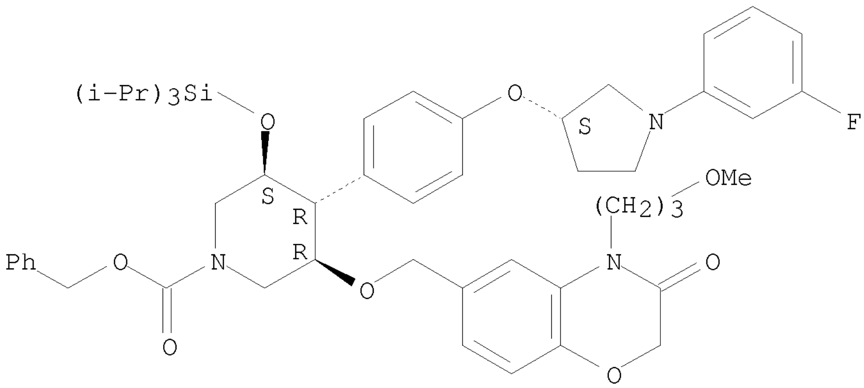
RN 873945-22-3 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[tris(1-methylethyl)silyl]oxy]-, phenylmethyl ester, (3R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 873945-23-4 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-3-oxo-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[tris(1-methylethyl)silyl]oxy]-, phenylmethyl ester, (3R,4R,5S)- (CA INDEX NAME)

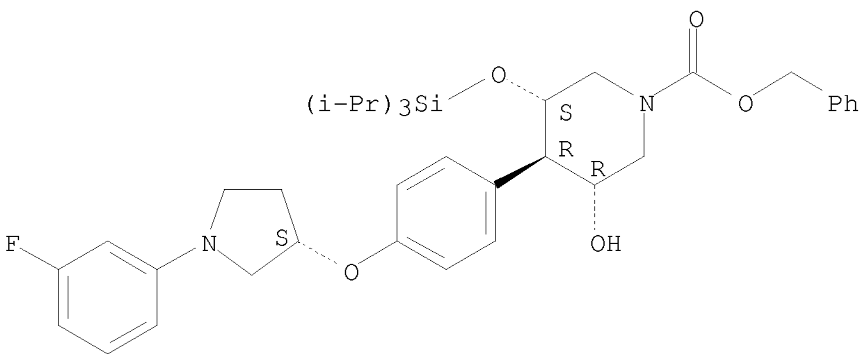
Absolute stereochemistry.



RN 873945-25-6 CAPLUS

CN 1-Piperidinecarboxylic acid, 4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-3-hydroxy-5-[[tris(1-methylethyl)silyl]oxy]-, phenylmethyl ester, (3R,4R,5S)- (CA INDEX NAME)

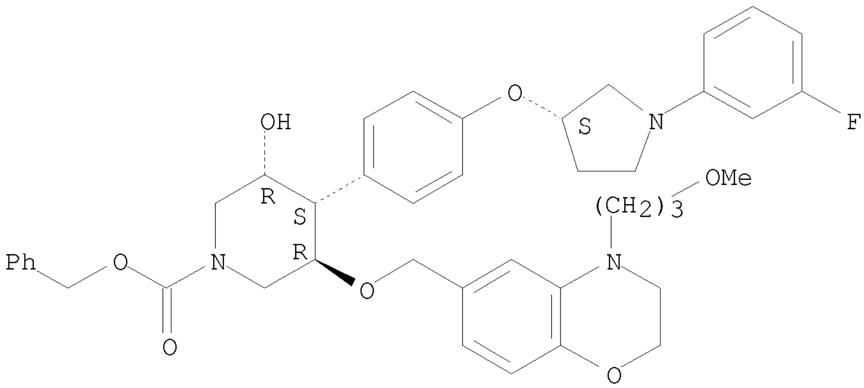
Absolute stereochemistry.



RN 873946-26-0 CAPLUS

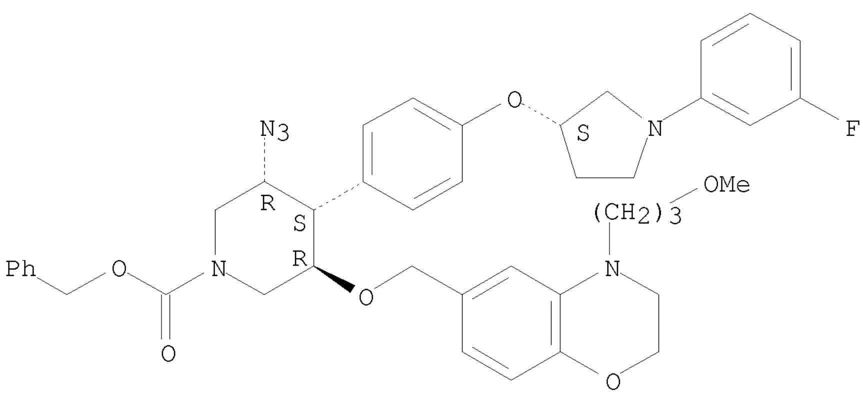
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, phenylmethyl ester, (3R,4S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



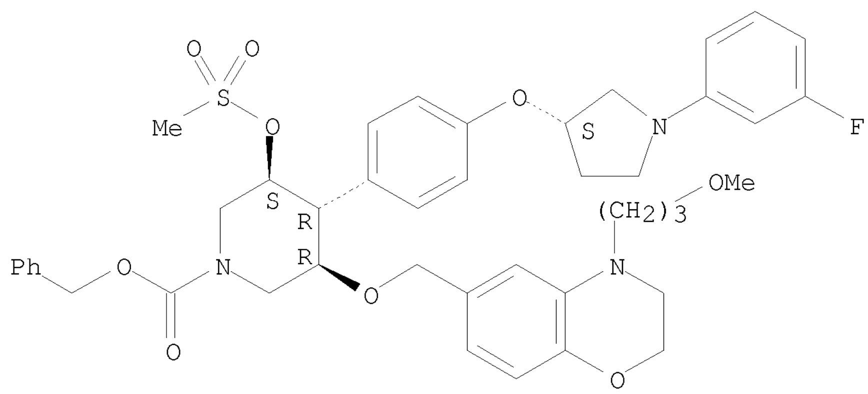
RN 873946-30-6 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-azido-5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-, phenylmethyl ester, (3R,4S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



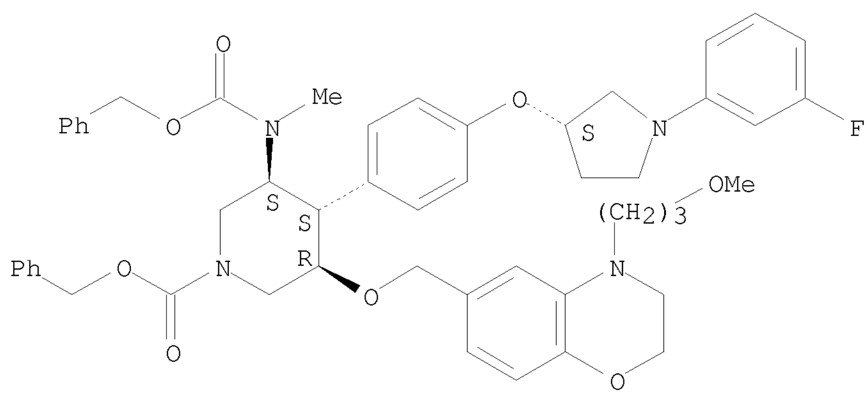
RN 873946-31-7 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[(methylsulfonyl)oxy]-, phenylmethyl ester, (3R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



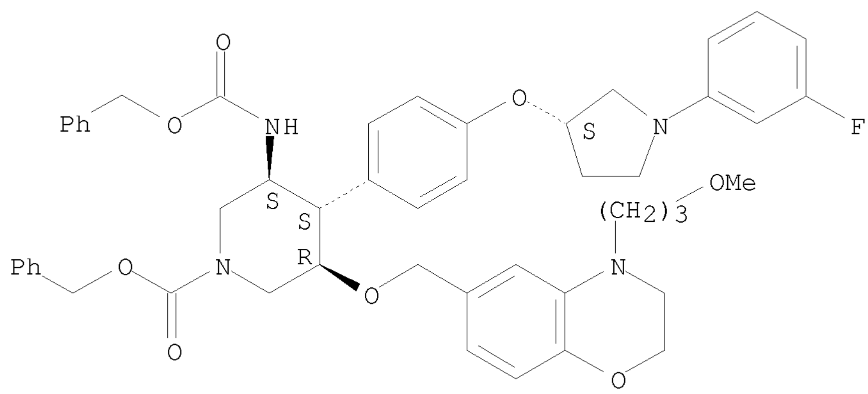
RN 873946-42-0 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[methyl[(phenylmethoxy)carbonyl]amino]-, phenylmethyl ester, (3R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 873946-43-1 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[(phenylmethoxy)carbonyl]amino]-, phenylmethyl ester, (3R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:1356517 CAPLUS
DOCUMENT NUMBER: 146:75295
TITLE: 1-{[4-(1-Azetidinylcarbonyl)phenyl]carbonyl}-4-(4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)piperidine and derivatives thereof, preparation, pharmaceutical compositions, and use for the treatment of inflammatory and allergic disorders
INVENTOR(S): Bamford, Mark James; Dean, David Kenneth; Hancock, Ashley Paul; Wilson, David Matthew
PATENT ASSIGNEE(S): UK
SOURCE: U.S. Pat. Appl. Publ., 13pp., Cont.-in-part of U.S. Ser. No. 551,985.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060293298	A1	20061228	US 2005-246480	20051007
WO 2004089373	A1	20041021	WO 2004-EP3985	20040408

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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060205774	A1	20060914	US 2005-551985	20051004
WO 2006125665	A1	20061130	WO 2006-EP5053	20060523

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             VN, YU, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM
     EP 1883636           A1    20080206    EP 2006-743071         20060523
         R:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, HR
     JP 2008542229        T     20081127    JP 2008-512778         20060523
PRIORITY APPLN. INFO.:                      GB 2003-8333        A  20030410
                                            WO 2004-EP3985      W  20040408
                                            GB 2005-10731       A  20050525
                                            US 2005-551985      A2 20051004
                                            US 2005-246480      A  20051007
                                            WO 2006-EP5053      W  20060523
OTHER SOURCE(S):         CASREACT 146:75295
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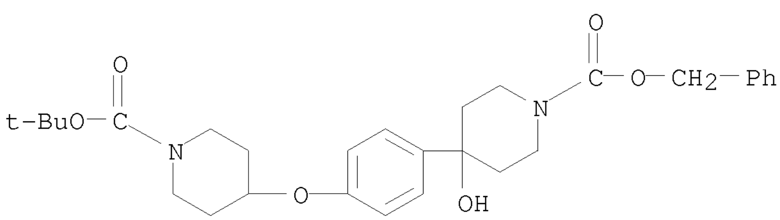
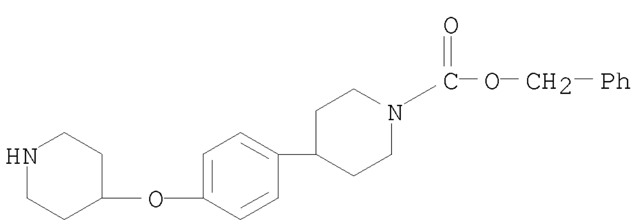
AB The invention relates to 1-{[4-(1-Azetidinylcarbonyl)phenyl]carbonyl}-4-(4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)piperidine and derivs. thereof, and to compns., processes for its preparation and its uses in therapy.

IT 778642-37-8P 915199-12-1P 915199-13-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(1-{[4-(1-Azetidinylcarbonyl)phenyl]carbonyl}-4-(4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)piperidine and derivs., preparation, pharmaceutical compns., and use for treatment of inflammatory and allergic disorders)

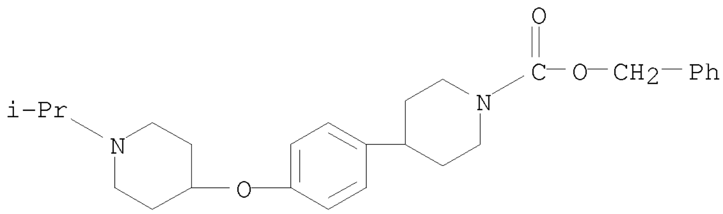
RN 778642-37-8 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[4-[[1-[(1,1-dimethylethoxy)carbonyl]-4-piperidinyl]oxy]phenyl]-4-hydroxy-, phenylmethyl ester (CA INDEX NAME)



RN 915199-12-1 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[4-(4-piperidinyloxy)phenyl]-, phenylmethyl ester (CA INDEX NAME)



RN 915199-13-2 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[4-[[1-(1-methylethyl)-4-piperidinyl]oxy]phenyl]-, phenylmethyl ester (CA INDEX NAME)



L4 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN

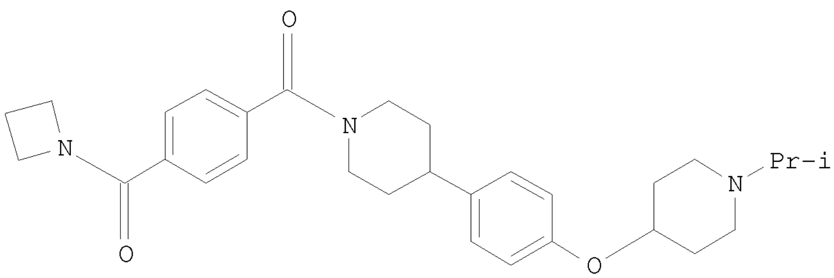
ACCESSION NUMBER: 2006:1251768 CAPLUS
DOCUMENT NUMBER: 145:505340
TITLE: Preparation of piperidine derivative as H1 receptor antagonist for treatment of allergic rhinitis
INVENTOR(S): Bamford, Mark James; Dean, David Kenneth; Hancock, Ashley Paul; Wilson, David Matthew
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 34pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006125665	A1	20061130	WO 2006-EP5053	20060523
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20060293298	A1	20061228	US 2005-246480	20051007
EP 1883636	A1	20080206	EP 2006-743071	20060523
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, HR				
JP 2008542229	T	20081127	JP 2008-512778	20060523

PRIORITY APPLN. INFO.:

APPLICATION NO.	KIND	DATE
GB 2005-10731	A	20050525
US 2005-246480	A	20051007
GB 2003-8333	A	20030410
WO 2004-EP3985	W	20040408
US 2005-551985	A2	20051004
WO 2006-EP5053	W	20060523

OTHER SOURCE(S): CASREACT 145:505340
GI



I

AB The title compound with structure I was prepared in a multistep synthesis from 4-(azetidin-1-ylcarbonyl)benzoic acid and 1-(1-methylethyl)-4-{[4-(4-piperidinyl)phenyl]oxy}piperidine (preparation given). I or pharmaceutically acceptable salts thereof are prepared as antagonist of H1 receptor for the treatment of various disorders, such as allergic rhinitis. I exhibited antagonistic activities with pKi values of 9.6 and 5.6, resp., against histamine H3 and H1. I also showed low CNS penetration and good oral bioavailability in male CD Sprague Dawley rats.

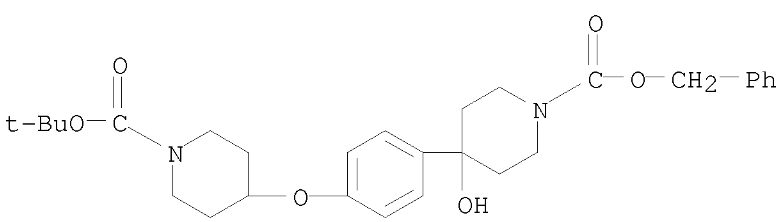
IT 778642-37-8P 915199-12-1P 915199-13-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of piperidine derivative as H1 receptor antagonist for treatment of allergic rhinitis)

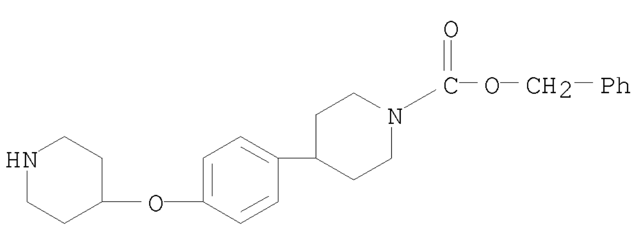
RN 778642-37-8 CAPLUS

CN 1-Piperidinecarboxylic acid, 4-[4-[[1-[(1,1-dimethylethoxy)carbonyl]-4-piperidinyl]oxy]phenyl]-4-hydroxy-, phenylmethyl ester (CA INDEX NAME)



RN 915199-12-1 CAPLUS

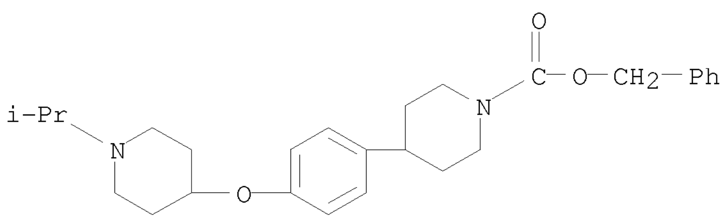
CN 1-Piperidinecarboxylic acid, 4-[4-(4-piperidinyloxy)phenyl]-, phenylmethyl ester (CA INDEX NAME)



RN 915199-13-2 CAPLUS

CN 1-Piperidinecarboxylic acid, 4-[4-[[1-(1-methylethyl)-4-

piperidinyl]oxy]phenyl]-, phenylmethyl ester (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:53811 CAPLUS
DOCUMENT NUMBER: 144:150244
TITLE: Preparation of 3-hydroxy/alkoxy-4-phenyl-5-alkoxypiperidines as renin inhibitors
INVENTOR(S): Herold, Peter; Mah, Robert; Stutz, Stefan; Stojanovic, Aleksandar; Tschinke, Vincenzo; Jotterand, Nathalie; Behnke, Dirk
PATENT ASSIGNEE(S): Speedel Experimenta A.-G., Switz.
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2006005741	A2	20060119	WO 2005-EP53306		20050711
WO 2006005741	A3	20060706			

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
CA 2570920	A1	20060119	CA 2005-2570920		20050711
EP 1776359	A2	20070425	EP 2005-761185		20050711

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
CN 101014594	A	20070808	CN 2005-80022749		20050711
JP 2008505871	T	20080228	JP 2007-519812		20050711
BR 2005013199	A	20080429	BR 2005-13199		20050711
IN 2006DN07870	A	20070817	IN 2006-DN7870		20061226
US 20080076766	A1	20080327	US 2007-631777		20070108
PRIORITY APPLN. INFO.:			CH 2004-1158	A	20040709
			WO 2005-EP53306	W	20050711

OTHER SOURCE(S): CASREACT 144:150244; MARPAT 144:150244
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

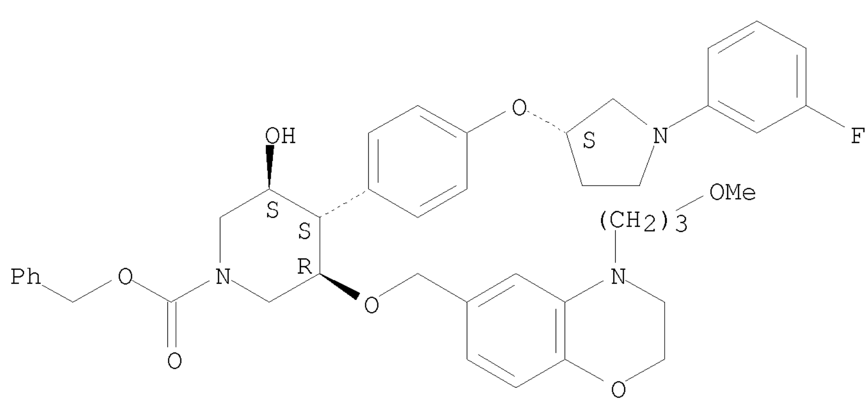
AB Title compds. I [R1 = aryl when R2 = (un)substituted tetrazolyl, imidazolyl; or R1 = (un)substituted aryl, heterocyclyl, etc.; R2 = (un)substituted Ph, naphthyl, cyclohexyl, pyrazinyl, tetrazolyl, etc.; R3 = H, OH, alkoxy, alkenyloxy; R4 = alkylcarbonylalkoxy/alkoxy, etc.; X = a bond, O, S, NH and derivs., OCO, etc.; V = [W]m; W = O, S; Y = [Z]n; Z = alk(en)ylene, hydroxyalkylidene, O, N, S, with provisos; n = 1 or, when X = OCO, n = 0-1; m = 0-1; and their salts, prodrugs, and compds. in which one or more atoms are replaced by their stable, non-radioactive isotopes, in particular pharmaceutically acceptable salts] were prepared as renin inhibitors. For example, II was prepared via O-alkylation of phenol III (preparation given) with 1-(3-fluorophenyl)pyrrolidin-(3R)-3-yl p-toluene-4-sulfonate (preparation given) and O-alkylation of the resulting hydroxypiperidine with 6-chloromethyl-4-(3-methoxypropyl)-4H-benzo[1,4]oxazin-3-one (preparation given). I were tested in vitro for renin inhibitory activity by measuring the reduction of the formation of angiotensin I in human plasma and exhibited inhibitory effects at min. concns. of about 10-6 to about 10-10 mol/l. I effectively reduced blood pressure in vivo when administered at doses of about 0.003 to about 0.3 mg/kg i.v. and at doses of about 0.3 to about 30 mg/kg p.o. to primates. I are useful for treating hypertension, heart and kidney failure (no data), glaucoma (no data), etc.

IT 873945-20-1P 873945-22-3P 873945-23-4P
873945-25-6P 873946-26-0P 873946-30-6P
873946-31-7P 873946-42-0P 873946-43-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of substituted piperidines as renin inhibitors)

RN 873945-20-1 CAPLUS

CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, phenylmethyl ester, (3R,4S,5S)- (CA INDEX NAME)

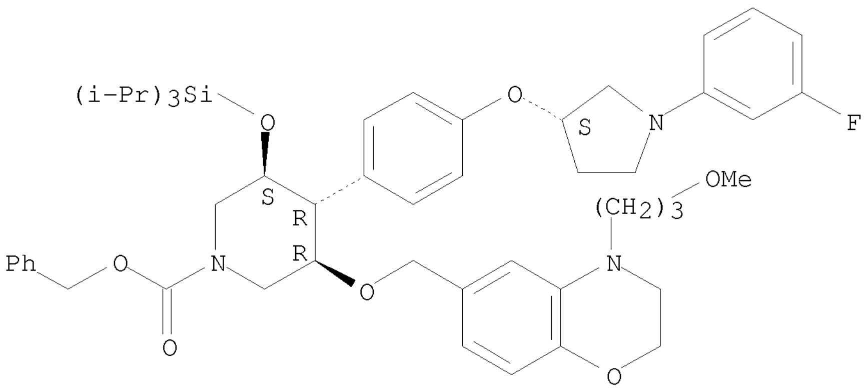
Absolute stereochemistry.



RN 873945-22-3 CAPLUS

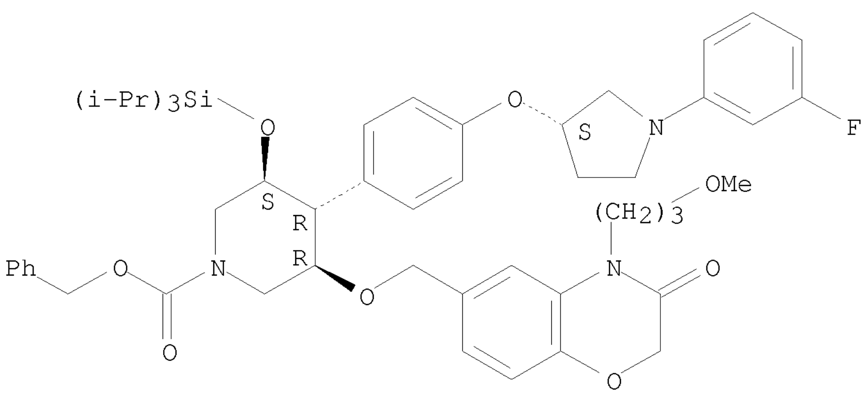
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[tris(1-methylethyl)silyl]oxy]-, phenylmethyl ester, (3R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



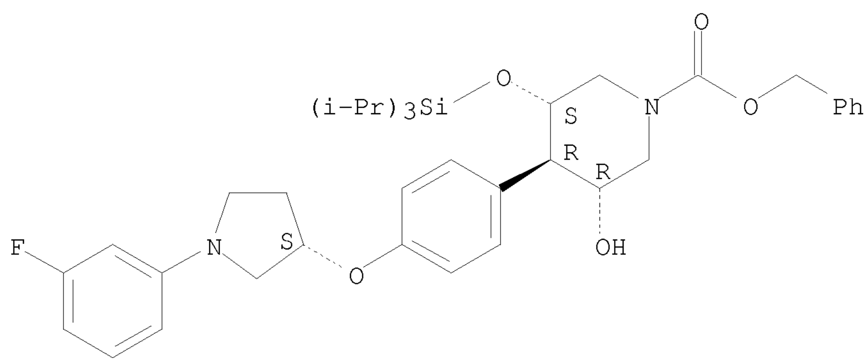
RN 873945-23-4 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-3-oxo-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[tris(1-methylethyl)silyl]oxy]-, phenylmethyl ester, (3R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



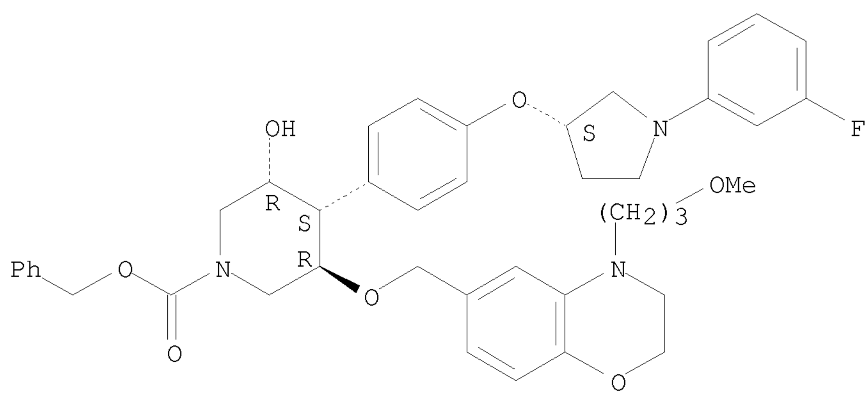
RN 873945-25-6 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-3-hydroxy-5-[[tris(1-methylethyl)silyl]oxy]-, phenylmethyl ester, (3R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



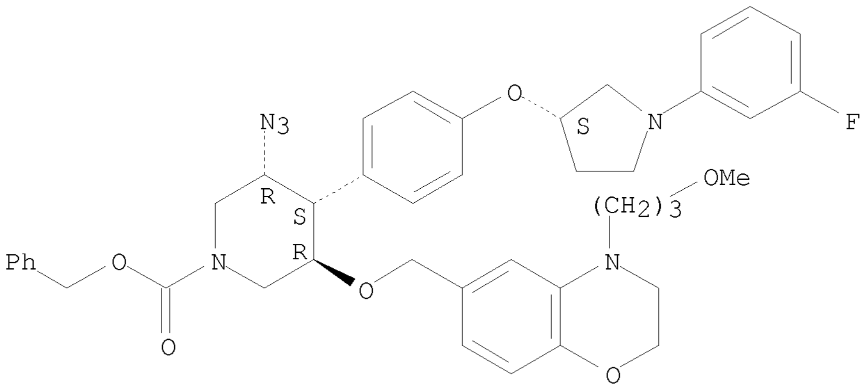
RN 873946-26-0 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-hydroxy-, phenylmethyl ester, (3R,4S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 873946-30-6 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-azido-5-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-, phenylmethyl ester, (3R,4S,5R)- (CA INDEX NAME)

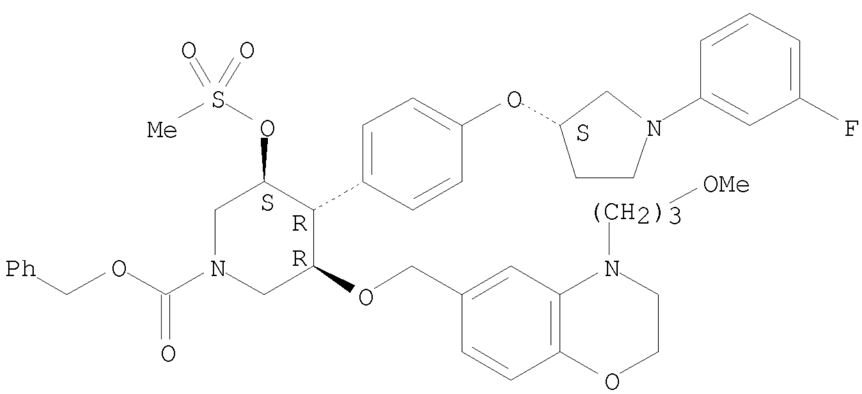
Absolute stereochemistry.



RN   873946-31-7 CAPLUS

CN   1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[(methylsulfonyl)oxy]-, phenylmethyl ester, (3R,4R,5S)- (CA INDEX NAME)

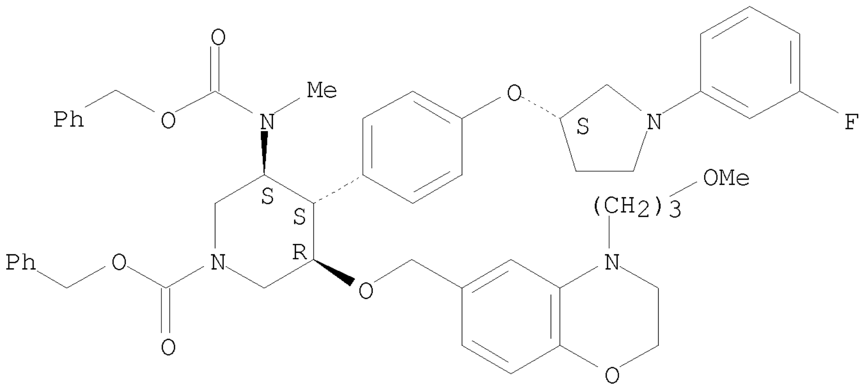
Absolute stereochemistry.



RN   873946-42-0 CAPLUS

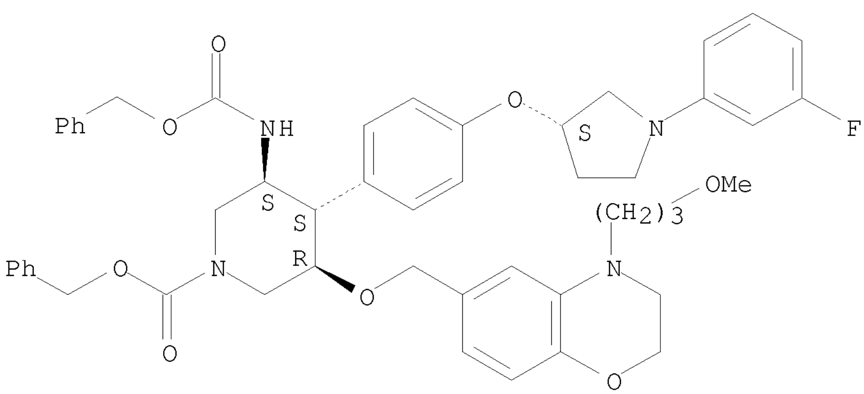
CN   1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[methyl[(phenylmethoxy)carbonyl]amino]-, phenylmethyl ester, (3R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 873946-43-1 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-(3-fluorophenyl)-3-pyrrolidinyl]oxy]phenyl]-5-[[(phenylmethoxy)carbonyl]amino]-, phenylmethyl ester, (3R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 10 CAPLUS

ACCESSION NUMBER: 2005:588898 CAPLUS
DOCUMENT NUMBER: 143:115449
TITLE: Preparation of piperidines as renin inhibitors useful against hypertension and other disorders
INVENTOR(S): Herold, Peter; Mah, Robert; Stutz, Stefan; Stojanovic, Aleksandar; Tschinke, Vincenzo; Jotterand, Nathalie
PATENT ASSIGNEE(S): Speedel Experimenta A.-G., Switz.
SOURCE: PCT Int. Appl., 252 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2005061457	A1	20050707	WO 2004-EP52389	20040930
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1670760	A1	20060621	EP 2004-820600	20040930
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
EP 1961752	A2	20080827	EP 2008-100929	20040930
EP 1961752	A3	20081119		
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
US 20070010511	A1	20070111	US 2006-574108	20060331
US 20090012055	A1	20090108	US 2008-68443	20080206

PRIORITY APPLN. INFO.:
CH 2003-1669 A 20031001
CH 2004-343 A 20040227
EP 2004-820600 A3 20040930
WO 2004-EP52389 W 20040930
US 2006-574108 A3 20060331

OTHER SOURCE(S): MARPAT 143:115449

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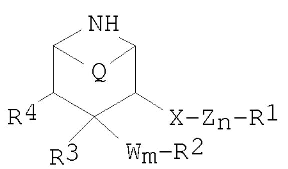
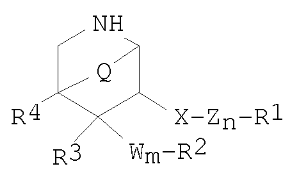
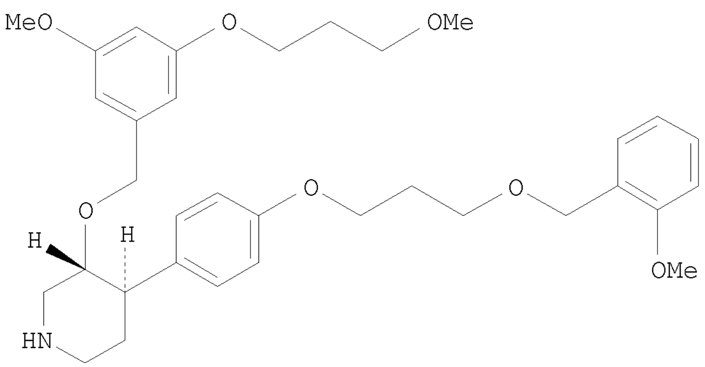


I



II



III

AB Novel substituted piperidines (shown as I and II; variables defined below; e.g. trans-4-[4-[3-(2-methoxybenzyloxy)propoxy]phenyl]-3-[[3-methoxy-5-(3-methoxypropoxy)benzyl]oxy]piperidine (shown as III)) are described. The compds. are suitable in particular as renin inhibitors and are highly potent. A test that measures the formation of angiotensin I in human

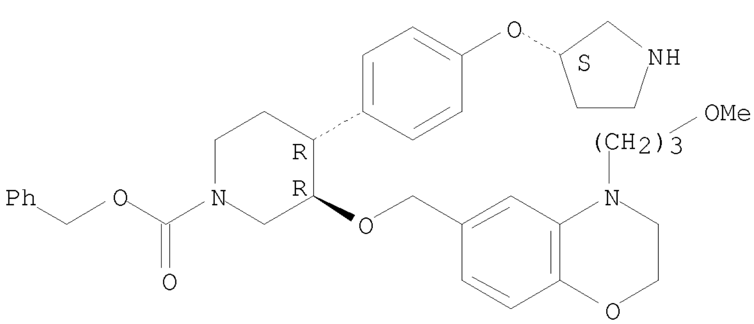
plasma revealed that I exhibit inhibiting actions in the in vitro systems at min. concns. of .apprx.10-6 to .apprx.10-10 mol/L. Compds. I effectively reduce blood pressure in an in vivo test involving normotensive marmosets at doses of .apprx.0.003 to .apprx.0.3 mg/kg i.v. and at doses of .apprx.0.3 to .apprx.30 mg/kg p.o. For I: R1 is (un)substituted oxazolyl, indolyl, pyrrolyl, pyrazolyl, triazinyl, 2-oxodihydrobenzo[d][1,3]oxazinyl, 4-oxodihydroimidazolyl, 5-oxo-4H-[1,2,4]triazinyl, 3-oxo-4H-benzo[1,4]thiazinyl, tetrahydroquinoxalinyl, 1,1,3-trioxodihydro-2H-1λ6-benzo[1,4]thiazinyl, 1-oxopyridyl, dihydro-2H-benzo[1,4]oxazinyl, 2-oxotetrahydrobenzo[e][1,4]diazepinyl, etc. For II: R1 is aryl or heteroaryl. For I and II: R2 is (un)substituted Ph, naphthyl, acenaphthyl, cyclohexyl, pyridyl, pyrimidinyl, pyrazinyl, oxopyridinyl, diazinyl, triazolyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, pyrrolyl, furyl, tetrazolyl or imidazolyl;. R3 is H, hydroxy, C1-6-alkoxy or C2-6-alkenyloxy; R4 is H, C1-6-alkyl, C2-6-alkenyl, C1-6-alkoxy, hydroxy-C1-6-alkyl, C1-6-alkoxy-C1-6-alkyl, benzyl, oxo, etc.; or R3 and R4 in I together are a bond. Q is ethylene or is absent for I or is ethylene or methylene for II; X is a bond, O or S, or is a >CHR11, >CHOR9, -OCO-, >CO, >C:NOR10, -OCHR11- or -OCHR11-CO-NR9- group and the bond starting from an O or S atom leads to a saturated C atom of the Z group or to R1; W is O or S; Z is C1-6-alkylene, C2-6-alkenylene, hydroxy-C1-6-alkylidene, -O-, -S-, -O-alk-, -S-alk-, -alk-O-, -alk-S- or -alk-NR9-, where alk is C1-6-alkylene; n = 0-1; m = 0-1; addnl. details including provisos are given in the claims. Although the methods of preparation are not claimed, example prepns. and/or characterization data for 360 I and II are included. For example, III was prepared from by deprotection of tert-Bu 4-[4-(3-benzyloxypropoxy)phenyl]-3-[[[3-(3-methoxypropoxy)phenyl]methyl]oxy]piperidine-1-carboxylate, which was prepared by ether formation between tert-Bu 3-hydroxy-4-[4-[3-(2-methoxybenzyloxy)propoxy]phenyl]piperidine-1-carboxylate and 1-chloromethyl-3-methoxy-5-(3-methoxypropoxy)benzene using NaH in DMF.

IT 857278-52-5, Benzyl (3R,4R)-3-[[4-(3-methoxypropyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]methoxy]-4-[4-[((S)-pyrrolidin-3-yl)oxy]phenyl]piperidine-1-carboxylate
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of piperidines as renin inhibitors useful against hypertension and other disorders)

RN 857278-52-5 CAPLUS

CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[(3S)-3-pyrrolidinyloxy]phenyl]-, phenylmethyl ester, (3R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



IT 857278-50-3P, Benzyl (3R,4R)-4-[4-[[(3S)-1-(2-

cyclopropylacetyl)pyrrolidin-3-yl]oxy]phenyl]-3-[[4-(3-methoxypropyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]methoxy]piperidine-1-carboxylate 857278-57-0P, Benzyl (3R,4R)-3-[[4-(3-methoxypropyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]methoxy]-4-[4-[((3S)-1-phenylpyrrolidin-3-yl)oxy]phenyl]piperidine-1-carboxylate 857278-58-1P, Benzyl (3R,4R)-3-[[4-(3-methoxypropyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]methoxy]-4-[4-[((3S)-1-phenylpyrrolidin-3-yl)oxy]phenyl]piperidine-1-carboxylate 857278-59-2P, Benzyl (3R,4R)-3-[[4-(3-methoxypropyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]methoxy]-4-[4-[((3S)-pyrrolidin-3-yl)oxy]phenyl]piperidine-1-carboxylate 857278-60-5P, Benzyl (3R,4R)-4-[4-[[(3S)-1-(tert-butoxycarbonyl)pyrrolidin-3-yl]oxy]phenyl]-3-[[4-(3-methoxypropyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]methoxy]piperidine-1-carboxylate 857278-61-6P, Benzyl (3R,4R)-4-[4-[[(3S)-1-(tert-butoxycarbonyl)pyrrolidin-3-yl]oxy]phenyl]-3-hydroxypiperidine-1-carboxylate 857279-89-1P, Benzyl (3R,4R)-4-[4-[((3S)-1-cyclohexylpyrrolidin-3-yl)oxy]phenyl]-3-[[4-(3-methoxypropyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]methoxy]piperidine-1-carboxylate 857279-90-4P, Benzyl (3R,4R)-4-[4-[((3S)-1-cyclohexylpyrrolidin-3-yl)oxy]phenyl]-3-[[4-(3-methoxypropyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]methoxy]piperidine-1-carboxylate 857280-03-6P, Benzyl (3R,4R)-3-[2-[2-[2-(acetylamino)ethyl]-5-fluorophenoxy]ethoxy]-4-[4-[((3S)-1-phenylpyrrolidin-3-yl)oxy]phenyl]piperidine-1-carboxylate 857280-04-7P, Benzyl (3R,4R)-3-[2-[2-[2-(acetylamino)ethyl]-5-fluorophenoxy]ethoxy]-4-[4-[((3S)-pyrrolidin-3-yl)oxy]phenyl]piperidine-1-carboxylate 857280-05-8P, Benzyl (3R,4R)-3-[2-[2-[2-(acetylamino)ethyl]-5-fluorophenoxy]ethoxy]-4-[4-[[(3S)-1-(tert-butoxycarbonyl)pyrrolidin-3-yl]oxy]phenyl]piperidine-1-carboxylate 857280-09-2P, Benzyl (3R,4R)-3-[[4-(3-methoxypropyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]methoxy]-4-[4-[((3S)-2-oxo-1-phenylpyrrolidin-3-yl)oxy]phenyl]piperidine-1-carboxylate

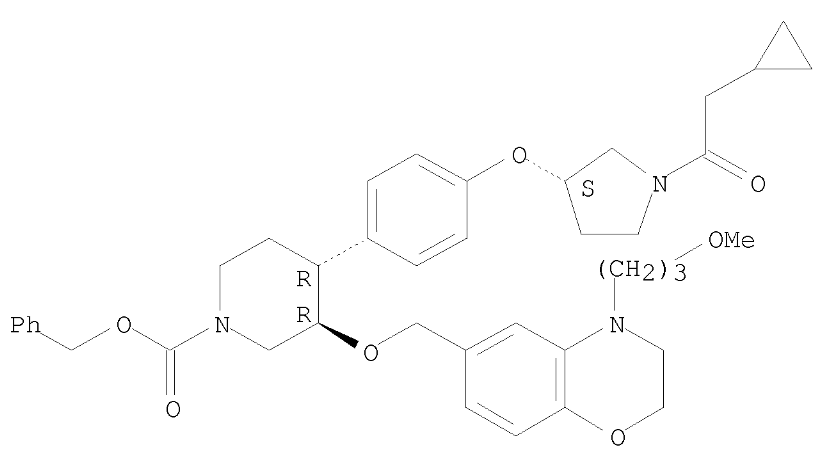
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of piperidines as renin inhibitors useful against hypertension and other disorders)

RN 857278-50-3 CAPLUS

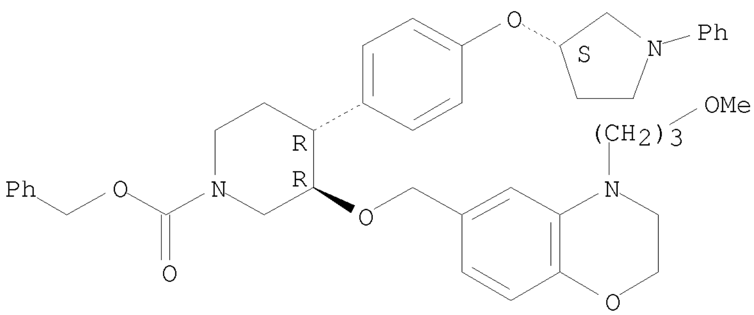
CN 1-Piperidinecarboxylic acid, 4-[4-[[(3S)-1-(2-cyclopropylacetyl)-3-pyrrolidinyl]oxy]phenyl]-3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-, phenylmethyl ester, (3R,4R)-rel- (CA INDEX NAME)

Relative stereochemistry.



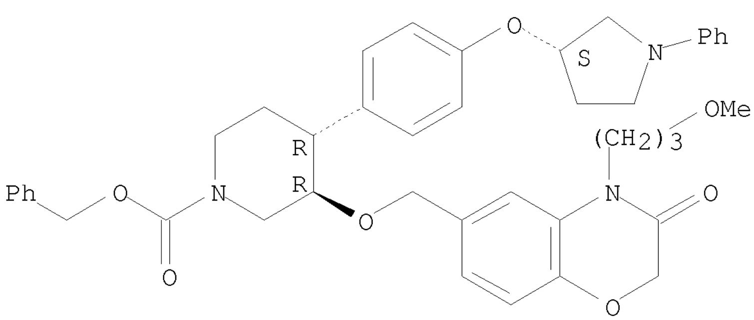
RN   857278-57-0 CAPLUS
CN   1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-phenyl-3-pyrrolidinyl]oxy]phenyl]-, phenylmethyl ester, (3R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



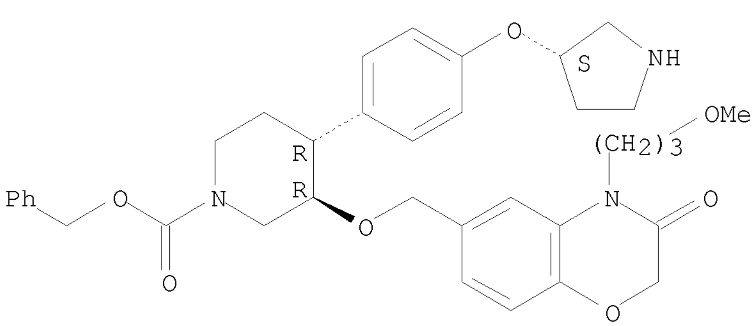
RN   857278-58-1 CAPLUS
CN   1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-3-oxo-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-phenyl-3-pyrrolidinyl]oxy]phenyl]-, phenylmethyl ester, (3R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



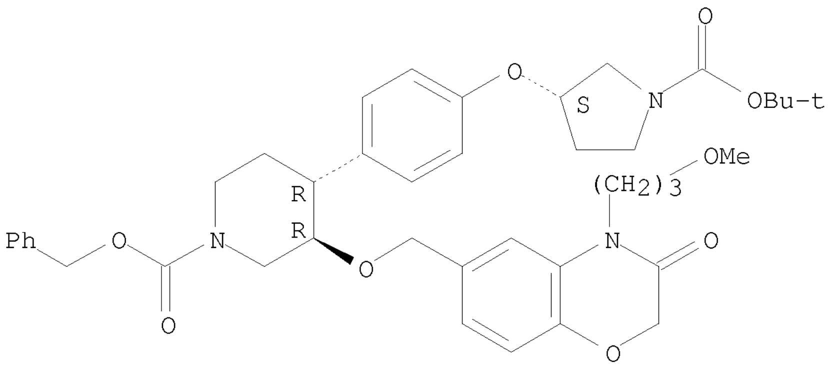
RN   857278-59-2 CAPLUS
CN   1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-3-oxo-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[(3S)-3-pyrrolidinyloxy]phenyl]-, phenylmethyl ester, (3R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



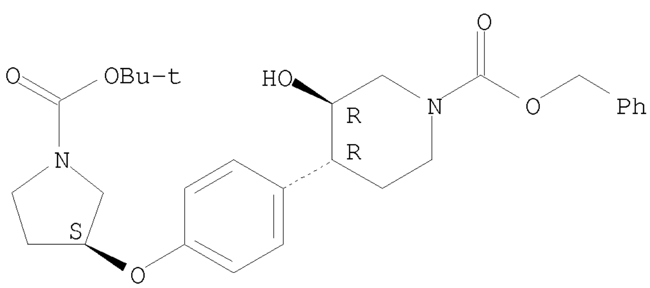
RN 857278-60-5 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-3-oxo-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-1-[(1,1-dimethylethoxy)carbonyl]-3-pyrrolidinyl]oxy]phenyl]-, phenylmethyl ester, (3R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



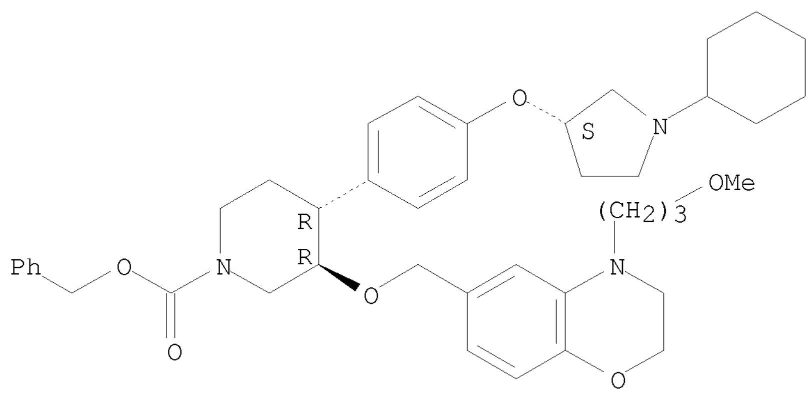
RN 857278-61-6 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[4-[[(3S)-1-[(1,1-dimethylethoxy)carbonyl]-3-pyrrolidinyl]oxy]phenyl]-3-hydroxy-, phenylmethyl ester, (3R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



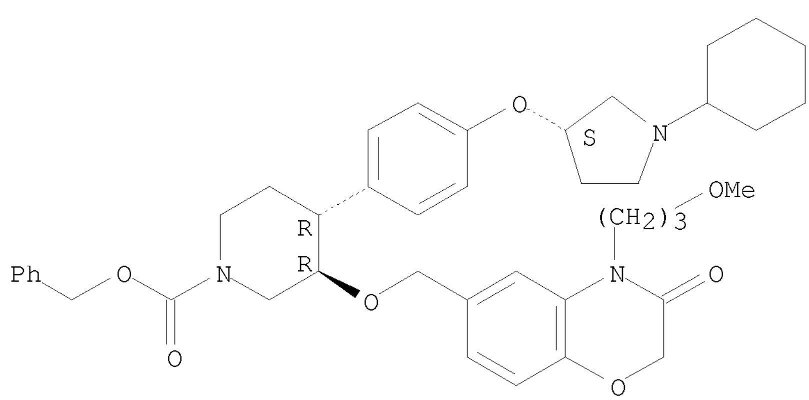
RN 857279-89-1 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[4-[[(3S)-1-cyclohexyl-3-pyrrolidinyl]oxy]phenyl]-3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-, phenylmethyl ester, (3R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



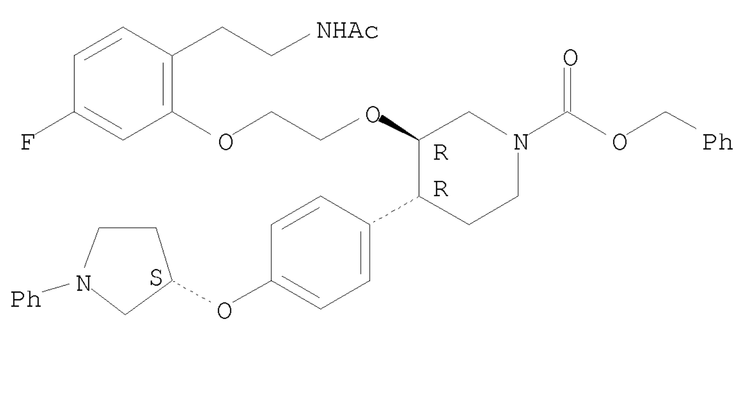
RN 857279-90-4 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[4-[[(3S)-1-cyclohexyl-3-pyrrolidinyl]oxy]phenyl]-3-[[3,4-dihydro-4-(3-methoxypropyl)-3-oxo-2H-1,4-benzoxazin-6-yl]methoxy]-, phenylmethyl ester, (3R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



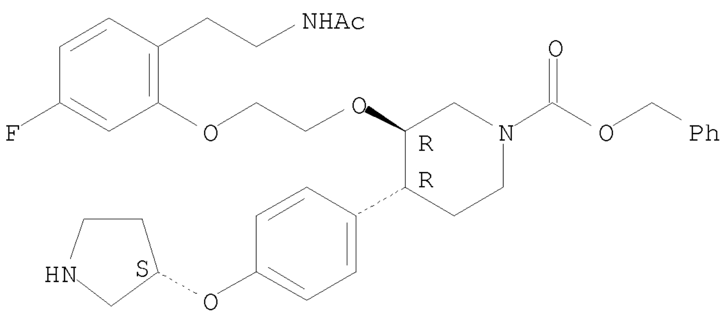
RN 857280-03-6 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[2-[2-[2-(acetylamino)ethyl]-5-fluorophenoxy]ethoxy]-4-[4-[[(3S)-1-phenyl-3-pyrrolidinyl]oxy]phenyl]-, phenylmethyl ester, (3R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



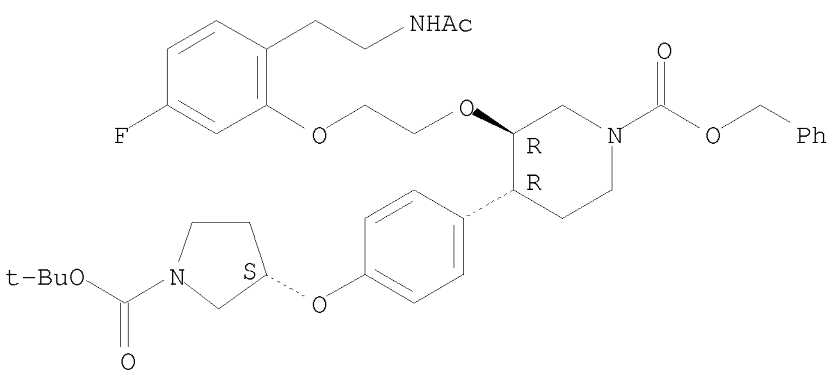
RN 857280-04-7 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[2-[2-[2-(acetylamino)ethyl]-5-fluorophenoxy]ethoxy]-4-[4-[(3S)-3-pyrrolidinyloxy]phenyl]-, phenylmethyl ester, (3R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



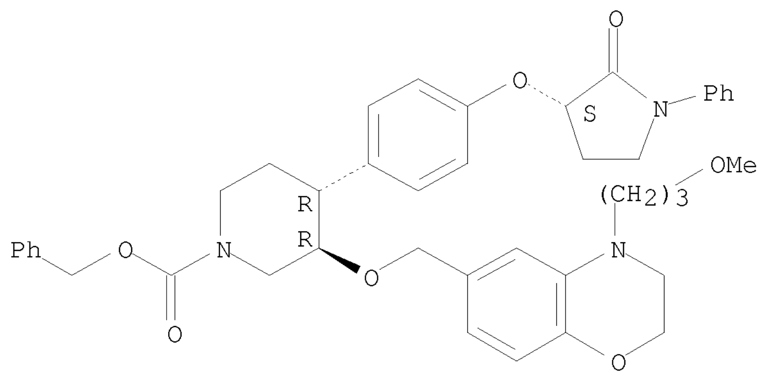
RN 857280-05-8 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[2-[2-[2-(acetylamino)ethyl]-5-fluorophenoxy]ethoxy]-4-[4-[[(3S)-1-[(1,1-dimethylethoxy)carbonyl]-3-pyrrolidinyl]oxy]phenyl]-, phenylmethyl ester, (3R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 857280-09-2 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[[(3S)-2-oxo-1-phenyl-3-pyrrolidinyl]oxy]phenyl]-, phenylmethyl ester, (3R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:878289 CAPLUS
DOCUMENT NUMBER: 141:366134
TITLE: Preparation of 4-(4-(heterocyclylalkoxy}phenyl)-1-(heterocyclyl-carbonyl)piperidine derivatives and related compounds as histamine H3 antagonists for the treatment of neurological diseases such as Alzheimer's
INVENTOR(S): Bamford, Mark James; Dean, David Kenneth; Wilson, David Matthew
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004228949	A1	20041021	AU 2004-228949	20040408
AU 2004228949	B2	20061102		
CA 2521899	A1	20041021	CA 2004-2521899	20040408
EP 1610786	A1	20060104	EP 2004-726514	20040408
EP 1610786	B1	20070620		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
BR 2004009110	A	20060328	BR 2004-9110	20040408
CN 1805747	A	20060719	CN 2004-80016195	20040408

JP 2006522771	T	20061005	JP 2006-505136		20040408
AT 365039	T	20070715	AT 2004-726514		20040408
ES 2288681	T3	20080116	ES 2004-726514		20040408
ZA 2005007795	A	20060726	ZA 2005-7795		20050927
IN 2005DN04435	A	20070928	IN 2005-DN4435		20050930
US 20060205774	A1	20060914	US 2005-551985		20051004
US 20060293298	A1	20061228	US 2005-246480		20051007
NO 2005005256	A	20060110	NO 2005-5256		20051109
PRIORITY APPLN. INFO.:			GB 2003-8333	A	20030410
			WO 2004-EP3985	W	20040408
			GB 2005-10731	A	20050525
			US 2005-551985	A2	20051004

OTHER SOURCE(S): MARPAT 141:366134

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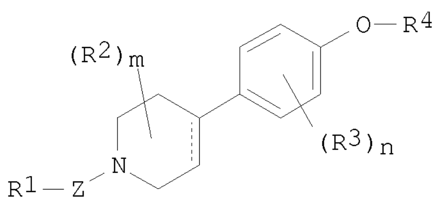

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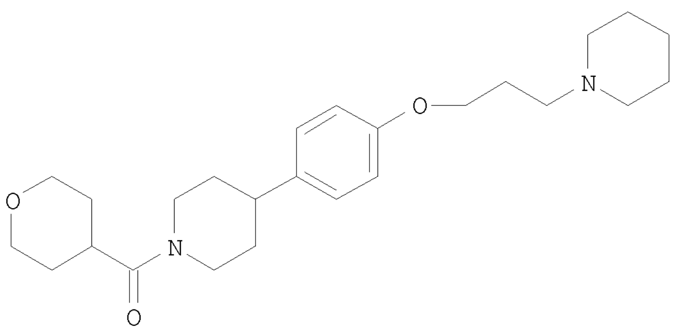


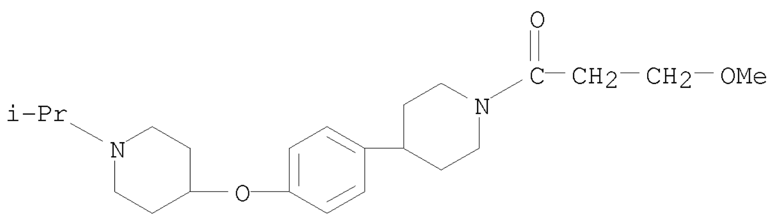
II

AB The present invention provides, in a first aspect, a compound of formula I [R1 = (un)substituted-C1-6alkyl-O-C1-6alkyl, -C3-8cycloalkyl, -aryl, -heterocyclyl, -heteroaryl, etc.; X = bond, O, CO, OCH2, CH2O or SO2; Z represents CO, CONR10 or SO2; R10 represents H, C1-6alkyl, -C3-8cycloalkyl, aryl, heterocyclyl, heteroaryl; m and n independently = 0, 1 or 2; R2 = H, C1-6alkyl or C1-6alkoxy; R3 represents halo, C1-6alkyl, OH, C1-6alkoxy, CN, amino, -COC1-6alkyl, -SO2C1-6alkyl or F3C; R4 = heterocyclyl or heterocyclylalkyl] or a pharmaceutically acceptable salt thereof, and methods to prepare I. Thus, e.g., II was prepared via amidation of 1-(3-{[4-(4-piperidinyl)phenyl]oxy}propyl)piperidine (preparation given) with tetrahydropyran-4-carboxylic acid. I and their pharmaceutically acceptable salts have affinity for and are antagonists and/or inverse agonists of the histamine H3 receptor and are believed to be of potential use in the treatment of neurol. diseases including Alzheimer's disease. I were tested in the histamine H3 functional antagonist assay and exhibited pKb values > 8.0.

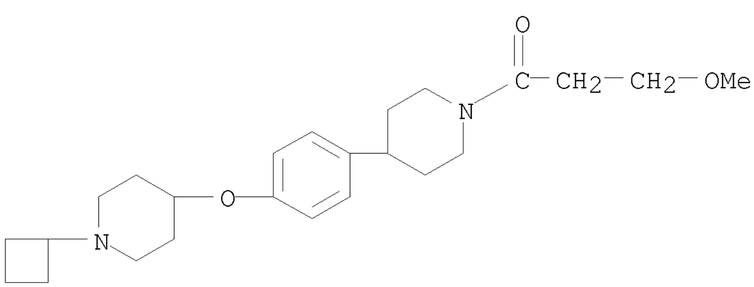
IT 778641-93-3P 778642-04-9P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

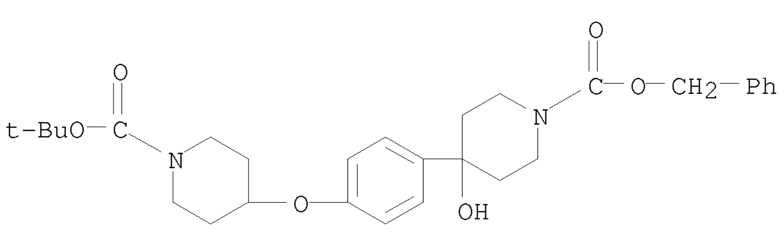
    (Uses)
       (drug candidate; preparation or arylpiperidine derivs. as histamine H3
       antagonists)
RN   778641-93-3 CAPLUS
CN   1-Propanone, 3-methoxy-1-[4-[4-[[1-(1-methylethyl)-4-
     piperidinyl]oxy]phenyl]-1-piperidinyl]- (CA INDEX NAME)



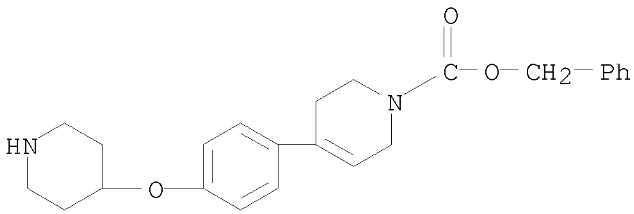
RN   778642-04-9 CAPLUS
CN   1-Propanone, 1-[4-[4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl]-1-
     piperidinyl]-3-methoxy- (CA INDEX NAME)



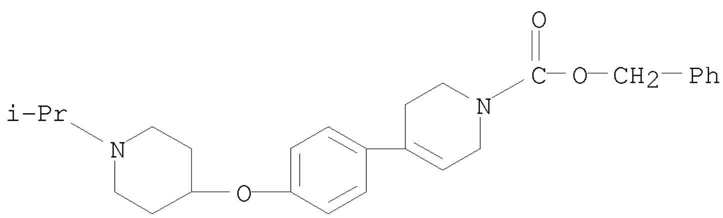
IT   778642-37-8P 778642-38-9P 778642-39-0P
     778642-41-4P 778642-45-8P
     RL: SPN (Synthetic preparation); PREP (Preparation)
       (intermediate; preparation or arylpiperidine derivs. as histamine H3
       antagonists)
RN   778642-37-8 CAPLUS
CN   1-Piperidinecarboxylic acid, 4-[4-[[1-[(1,1-dimethylethoxy)carbonyl]-4-
     piperidinyl]oxy]phenyl]-4-hydroxy-, phenylmethyl ester (CA INDEX NAME)



RN   778642-38-9 CAPLUS
CN   1(2H)-Pyridinecarboxylic acid, 3,6-dihydro-4-[4-(4-piperidinyloxy)phenyl]-
     , phenylmethyl ester (CA INDEX NAME)



RN   778642-39-0 CAPLUS
CN   1(2H)-Pyridinecarboxylic acid, 3,6-dihydro-4-[4-[[1-(1-methylethyl)-4-piperidinyl]oxy]phenyl]-, phenylmethyl ester (CA INDEX NAME)



RN   778642-41-4 CAPLUS
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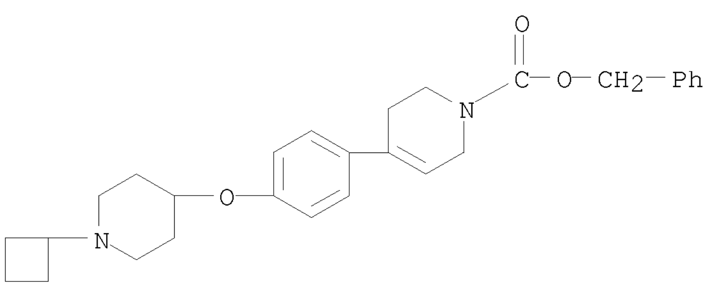
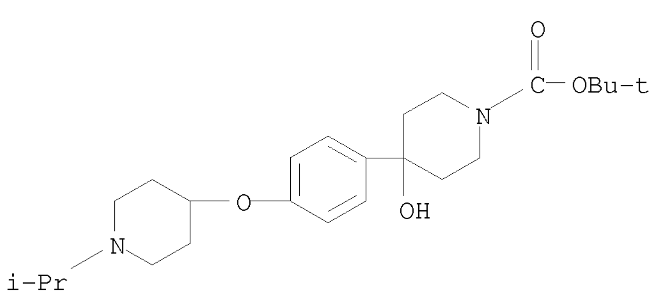


RN   778642-45-8 CAPLUS
CN   1-Piperidinecarboxylic acid, 4-hydroxy-4-[4-[[1-(1-methylethyl)-4-piperidinyl]oxy]phenyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)



REFERENCE COUNT: 4   THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L2              3 S L1
L3            126 S L1 FULL

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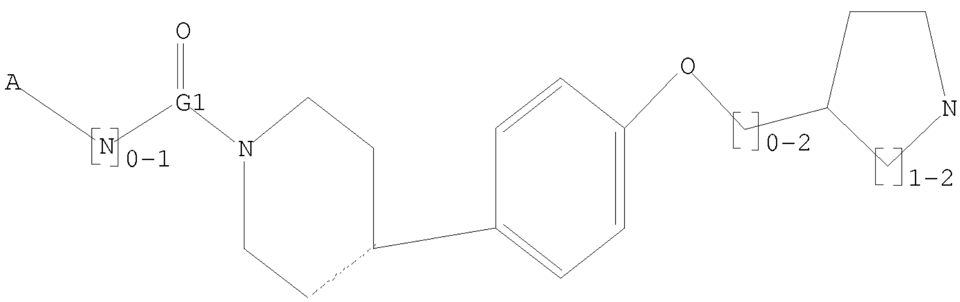

G1 C,S

Structure attributes must be viewed using STN Express query preparation.

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L8   ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2008:1217060  CAPLUS
DOCUMENT NUMBER:          149:425982
TITLE:                    Preparation of benzothiophenylpiperazine derivatives
                          for treatment of central nervous system diseases
INVENTOR(S):              Yamashita, Hiroshi; Matsubara, Atsushi; Oshima, Kunio;
                          Kuroda, Hideaki; Ito, Nobuaki; Miyamura, Shin;
                          Shimizu, Satoshi; Tanaka, Tatsuyoshi; Taira, Shinichi;
                          Kondo, Hitomi; Itotani, Motohiro; Fukushima, Tae;
                          Takahashi, Hisashi; Sakurai, Yoji; Kuroda, Takeshi
PATENT ASSIGNEE(S):       Ohtsuka Pharmaceutical Co., Ltd., Japan
SOURCE:                   Jpn. Kokai Tokkyo Koho, 454pp.
                          CODEN: JKXXAF
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2008239617	A	20081009	JP 2008-45563	20080227

PRIORITY APPLN. INFO.: JP 2007-46887 A 20070227

OTHER SOURCE(S): MARPAT 149:425982

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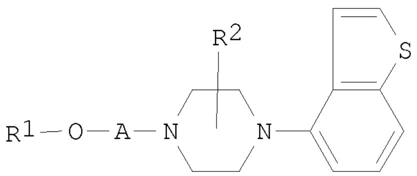


I

AB The title compds. I [R1 = (un)substituted cycloalkyl, (un)substituted aromatic ring, (un)substituted heterocyclic ring; R2 = H, alkyl; A = alkylene, alkenylene] are prepared Thus, 5-[3-[4-benzo[b]thiophen-4-ylpiperazin-1-yl]propoxy]-1-methyl-1H-pyrazole-3-carboxylic acid Me ester was prepared from 5-(3-chloropropoxy)-1-methyl-1H-pyrazole-3-carboxylic acid Me ester and 1-benzo[b]thiophen-4-ylpiperazine hydrochloride. In a dopamine D2 receptor binding assay, compds. of this invention showed Ki values of 0.2 to 5 nM. The title compds. I [R1 = (un)substituted cycloalkyl, (un)substituted aromatic ring, (un)substituted heterocyclic ring; R2 = H, alkyl; A = alkylene, alkenylene] were prepared Thus, 5-[3-[4-benzo[b]thiophen-4-ylpiperazin-1-yl]propoxy]-1-methyl-1H-pyrazole-3-carboxylic acid Me ester was prepared from 5-(3-chloropropoxy)-1-methyl-1H-pyrazole-3-carboxylic acid Me ester and 1-benzo[b]thiophen-4-ylpiperazine hydrochloride. In a dopamine D2 receptor binding assay, compds. of this invention showed Ki values of 0.2 to 5 nM.

IT 928226-28-2P

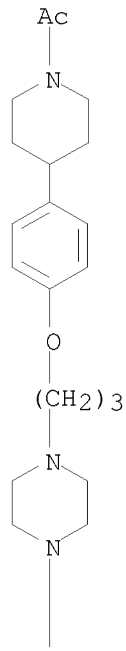
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of benzo[b]thiophen-4-yl-piperazine and related compds. as antipsychotic agents for the treatment of mental disorders)

RN 928226-28-2 CAPLUS

CN Ethanone, 1-[4-[4-[3-(4-benzo[b]thien-4-yl-1-piperazinyl)propoxy]phenyl]-1-piperidinyl]- (CA INDEX NAME)

PAGE 1-A



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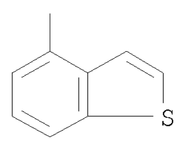

L8 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2007:705802 CAPLUS

DOCUMENT NUMBER: 147:95560

TITLE: Preparation of 3-[4-[[4-[4-[[3-(3,3-dimethyl-1-piperidinyl)propyl]oxy]phenyl]-1-piperidinyl]carbonyl]-1-naphthalenyl]propanoates as histamine H1 and H3 antagonists for the treatment of inflammatory and/or allergic disorders.

INVENTOR(S): Hodgson, Simon Teanby; Procopiou, Panayiotis Alexandrou; Vinader Brugarolas, Maria Victoria

PATENT ASSIGNEE(S): Glaxo Group Limited, UK

SOURCE: PCT Int. Appl., 62pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

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             GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN,
             KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK,
             MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
             RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT,
             TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
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             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM
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     EP 1963307             A1    20080903    EP 2006-841477         20061219
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     US 20080312280         A1    20081218    US 2008-158185         20080619
     CN 101341146           A     20090107    CN 2006-80048106       20080619
     IN 2008KN02485         A     20090123    IN 2008-KN2485         20080619
     MX 2008008141          A     20080704    MX 2008-8141           20080620
     KR 2008087102          A     20080930    KR 2008-715535         20080626
PRIORITY APPLN. INFO.:                        GB 2005-25897       A  20051220
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OTHER SOURCE(S):          MARPAT 147:95560
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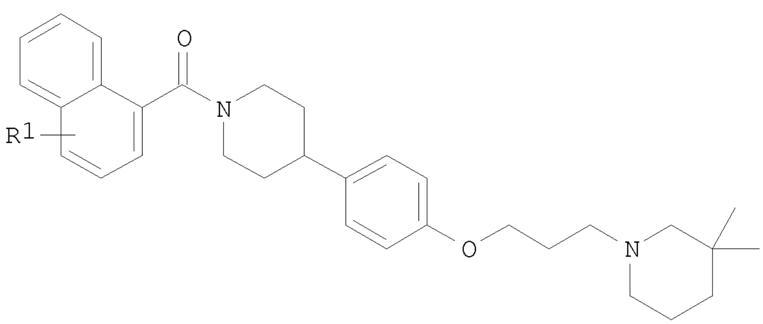


I

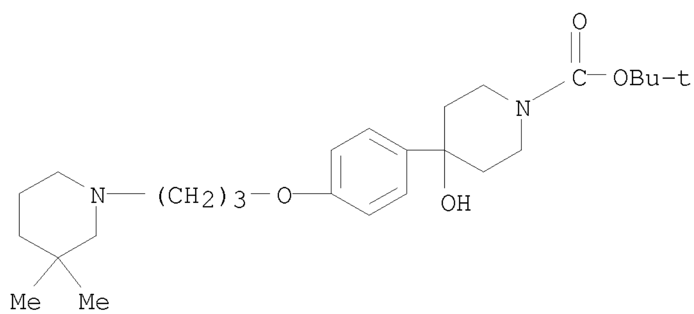
AB Title compds. (I; R1 = CH2CH2COOH, CH:CMeCO2H), were prepared Thus, 3-[4-[[4-[4-[[3-(3,3-dimethyl-1-piperidinyl)propyl]oxy]phenyl]-1-piperidinyl]carbonyl]-1-naphthalenyl]propanoic acid formate salt (multistep preparation given) showed histamine H3 antagonist activity with pKi = 7.4.

IT 942260-15-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of methylpiperidinylpropyloxyphenylpiperidinylcarbonylnaphthalenylpropanoates as H1 and H3 antagonists for the treatment of inflammatory and/or allergic disorders)

RN 942260-15-3 CAPLUS

CN 1-Piperidinecarboxylic acid, 4-[4-[3-(3,3-dimethyl-1-

piperidinyl)propoxy]phenyl]-4-hydroxy-, 1,1-dimethylethyl ester (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:257347 CAPLUS
DOCUMENT NUMBER: 146:316939
TITLE: Preparation of benzo[b]thiophen-4-yl-piperazine and related compounds as antipsychotic agents for the treatment of mental disorders
INVENTOR(S): Yamashita, Hiroshi; Matsubara, Jun; Oshima, Kunio; Kuroda, Hideaki; Ito, Nobuaki; Miyamura, Shin; Shimizu, Satoshi; Tanaka, Tatsuyoshi; Taira, Shinichi; Kondo, Kazumi; Itotani, Motohiro; Bando, Masahiko; Fukushima, Tae; Oshiro, Yasuo; Takahashi, Haruka; Sakurai, Yohji; Kuroda, Takeshi; Shimada, Jun; Maeda, Kenji; Tadori, Yoshihiro; Amada, Naoki; Akazawa, Hitomi; Yamashita, Junko; Mori, Atsushi; Uwahodo, Yasufumi; Masumoto, Takumi; Sugino, Haruhiko; Kikuchi, Tetsuro; Hashimoto, Kazuya
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 686pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007026959	A2	20070308	WO 2006-JP317704	20060831
WO 2007026959	A3	20070816		

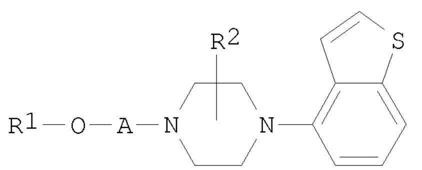
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

AU 2006285607	A1	20070308	AU 2006-285607		20060831
CA 2620688	A1	20070308	CA 2006-2620688		20060831
JP 2007091733	A	20070412	JP 2006-235401		20060831
EP 1919907	A2	20080514	EP 2006-797580		20060831
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR					
IN 2008DN01407	A	20080808	IN 2008-DN1407		20080219
KR 2008033446	A	20080416	KR 2008-704418		20080225
MX 2008002736	A	20080326	MX 2008-2736		20080226
CN 101258147	A	20080903	CN 2006-80032043		20080229
PRIORITY APPLN. INFO.:			JP 2005-251055	A	20050831
			WO 2006-JP17704	W	20060831
			WO 2006-JP317704	W	20060831

OTHER SOURCE(S): MARPAT 146:316939

GI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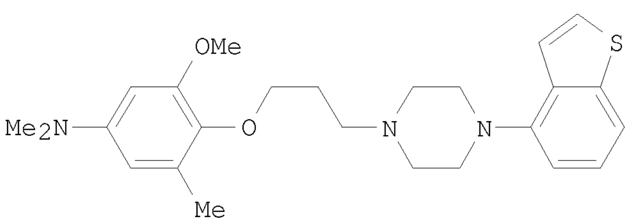

II

AB Title compds. I [R1 = cycloalkyl, (un)substituted aryl, heterocyclyl; R2 = H or lower alkyl; A = lower alkylene or lower alkenylene], and their pharmaceutically acceptable salts, are prepared and disclosed as antipsychotic agents for the treatment of mental disorders. Thus, e.g., II·HCl was prepared via nucleophilic substitution of [4-(3-chloropropoxy)-3-methoxy-5-methylphenyl]-carbamic acid tert-Bu ester (preparation given) with 1-benzo[b]thiophen-4-yl-piperazine hydrochloride (preparation given) followed by deprotection and dimethylation. Binding assays were used to determine Ki values for I, e.g., II·HCl demonstrated Ki values of 0.4 nM in Dopamine D2 receptor and 5.9 nM in Serotonin 5-HT2A receptor. Serotonin uptake inhibitory activity of II·HCl was also determined as 95.3%. The invention compds. may be widely used in the treatment and prevention of mental disorders including central nervous system disorders, while demonstrating no side effects.

IT 928226-28-2P

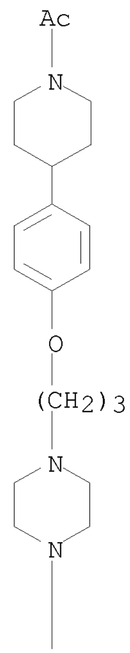
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of benzo[b]thiophen-4-yl-piperazine and related compds. as antipsychotic agents for the treatment of mental disorders)

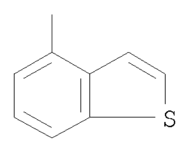
RN 928226-28-2 CAPLUS

CN Ethanone, 1-[4-[4-[3-(4-benzo[b]thien-4-yl-1-piperazinyl)propoxy]phenyl]-1-piperidinyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



L8 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2005:1220275 CAPLUS

DOCUMENT NUMBER: 143:460031

TITLE: Preparation of heterocycle-containing phenol ethers, thioethers and related derivatives as histamine H3 ligands

INVENTOR(S): Bernardelli, Patrick; Cronin, Andrew Michael; Denis, Alexis; Denton, Stephen Martin; Jacobelli, Henry; Kemp, Mark Ian; Lorthiois, Edwige; Rousseau, Fiona; Serradeil-Civit, Delphine; Vergne, Fabrice

PATENT ASSIGNEE(S): Warner-Lambert Company LLC, USA

SOURCE: PCT Int. Appl., 216 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005108384	A1	20051117	WO 2005-IB1114	20050419

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1593679	A1	20051109	EP 2004-291187	20040507

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR

AU 2005240846	A1	20051117	AU 2005-240846	20050419
CA 2565852	A1	20051117	CA 2005-2565852	20050419
EP 1747210	A1	20070131	EP 2005-718521	20050419

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU

CN 1950351	A	20070418	CN 2005-80014662	20050419
BR 2005010664	A	20071204	BR 2005-10664	20050419
JP 2007536365	T	20071213	JP 2007-512541	20050419
JP 4173191	B2	20081029		
KR 2006133091	A	20061222	KR 2006-723284	20061106
KR 843848	B1	20080703		
MX 2006012819	A	20070126	MX 2006-12819	20061106

PRIORITY APPLN. INFO.:

EP 2004-291187	A	20040507
GB 2005-4564	A	20050304
WO 2005-IB1114	W	20050419

OTHER SOURCE(S): CASREACT 143:460031; MARPAT 143:460031

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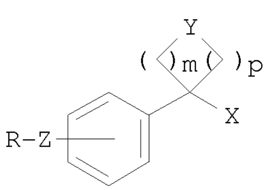

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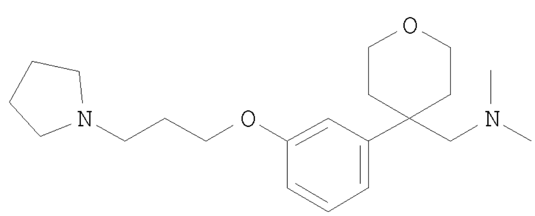


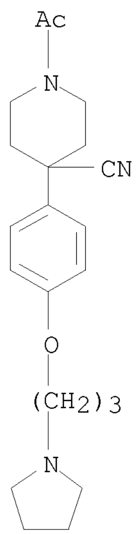
II

AB Title compds. [I; m, p = 0-3; m+p $\leq$4; X = cyano, CH2OH, alkoxymethyl, CO2H, alkoxycarbonyl, aminomethyl, aminocarbonyl, CH2Ohet (het = (substituted) mono- or bicyclic heteroaryl), CH2het, het; Y = CH2, CH(OH), CO, N (substituted by H, at al.); ZR is in the meta or para position of the Ph group; Z = O, S, S(O), S(O)2; R = (cyclo)aminoalkyl; addnl. details are given in the claims], were prepared Thus, reaction of 3-[4-(dimethylamino)methyltetrahydro-2H-pyran-4-yl]phenol (preparation given) with 1-(3-chloropropyl)pyrrolidine (preparation given) gave 20% title compound (II). In a cell-based H3 functional assay measuring cAMP through β-lactamase reporter gene activity, I showed Ki <5 μM; values are tabulated for 26 examples of I. I are H3 ligands useful in treating e.g. inflammatory, allergic and respiratory diseases.

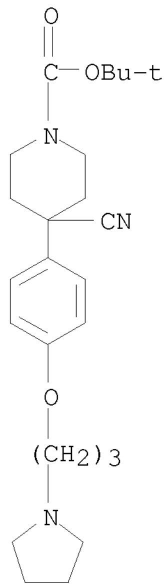
IT 869225-71-8P, 1-Acetyl-4-[4-[3-(pyrrolidin-1-yl)propoxy]phenyl]piperidine-4-carbonitrile

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)
(claimed compound; preparation of heterocycle-containing phenol ethers, thioethers
and related derivs. as histamine H3 ligands)
RN 869225-71-8 CAPLUS
CN 4-Piperidinecarbonitrile, 1-acetyl-4-[4-[3-(1-pyrrolidinyl)propoxy]phenyl]-
(CA INDEX NAME)



IT 869225-69-4P, tert-Butyl 4-cyano-4-[4-[3-(pyrrolidin-1-
yl)propoxy]phenyl]piperidine-1-carboxylate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation of heterocycle-containing phenol ethers, thioethers and related
derivs. as histamine H3 ligands)
RN 869225-69-4 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-cyano-4-[4-[3-(1-
pyrrolidinyl)propoxy]phenyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:588898 CAPLUS
DOCUMENT NUMBER: 143:115449
TITLE: Preparation of piperidines as renin inhibitors useful against hypertension and other disorders
INVENTOR(S): Herold, Peter; Mah, Robert; Stutz, Stefan; Stojanovic, Aleksandar; Tschinke, Vincenzo; Jotterand, Nathalie
PATENT ASSIGNEE(S): Speedel Experimenta A.-G., Switz.
SOURCE: PCT Int. Appl., 252 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005061457	A1	20050707	WO 2004-EP52389	20040930
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1670760	A1	20060621	EP 2004-820600	20040930
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
EP 1961752	A2	20080827	EP 2008-100929	20040930

EP 1961752	A3	20081119			
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR					
US 20070010511	A1	20070111	US 2006-574108		20060331
US 20090012055	A1	20090108	US 2008-68443		20080206
PRIORITY APPLN. INFO.:			CH 2003-1669	A	20031001
			CH 2004-343	A	20040227
			EP 2004-820600	A3	20040930
			WO 2004-EP52389	W	20040930
			US 2006-574108	A3	20060331

OTHER SOURCE(S): MARPAT 143:115449

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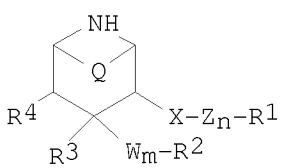

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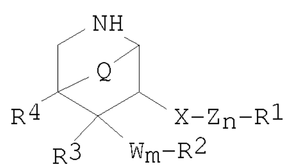

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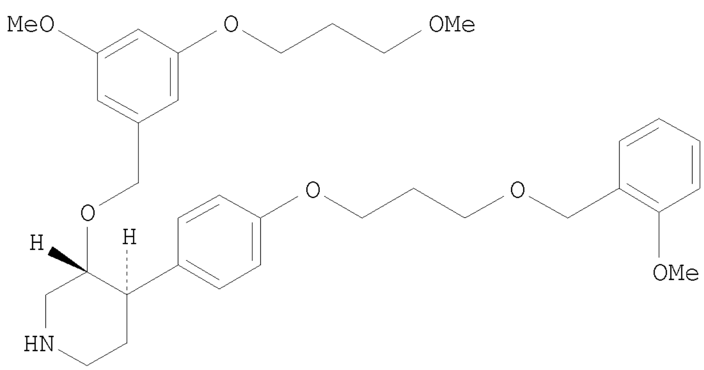


III

AB Novel substituted piperidines (shown as I and II; variables defined below; e.g. trans-4-[4-[3-(2-methoxybenzyloxy)propoxy]phenyl]-3-[[3-methoxy-5-(3-methoxypropoxy)benzyl]oxy]piperidine (shown as III)) are described. The compds. are suitable in particular as renin inhibitors and are highly potent. A test that measures the formation of angiotensin I in human plasma revealed that I exhibit inhibiting actions in the in vitro systems at min. concns. of .apprx.10-6 to .apprx.10-10 mol/L. Compds. I effectively reduce blood pressure in an in vivo test involving normotensive marmosets at doses of .apprx.0.003 to .apprx.0.3 mg/kg i.v. and at doses of .apprx.0.3 to .apprx.30 mg/kg p.o. For I: R1 is (un)substituted oxazolyl, indolyl, pyrrolyl, pyrazolyl, triazinyl, 2-oxodihydrobenzo[d][1,3]oxazinyl, 4-oxodihydroimidazolyl, 5-oxo-4H-[1,2,4]triazinyl, 3-oxo-4H-benzo[1,4]thiazinyl, tetrahydroquinoxalinyl, 1,1,3-trioxodihydro-2H-1λ6-benzo[1,4]thiazinyl, 1-oxopyridyl, dihydro-2H-benzo[1,4]oxazinyl, 2-oxotetrahydrobenzo[e][1,4]diazepinyl, etc. For II: R1 is aryl or heteroaryl. For I and II: R2 is (un)substituted Ph, naphthyl, acenaphthyl, cyclohexyl, pyridyl, pyrimidinyl, pyrazinyl, oxopyridinyl, diazinyl, triazolyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, pyrrolyl, furyl, tetrazolyl or imidazolyl;. R3 is H, hydroxy, C1-6-alkoxy or C2-6-alkenyloxy; R4 is H, C1-6-alkyl, C2-6-alkenyl, C1-6-alkoxy, hydroxy-C1-6-alkyl, C1-6-alkoxy-C1-6-alkyl, benzyl, oxo, etc.; or R3 and

R4 in I together are a bond. Q is ethylene or is absent for I or is ethylene or methylene for II; X is a bond, O or S, or is a >CHR11, >CHOR9, -OCO-, >CO, >C:NOR10, -OCHR11- or -OCHR11-CO-NR9- group and the bond starting from an O or S atom leads to a saturated C atom of the Z group or to R1; W is O or S; Z is C1-6-alkylene, C2-6-alkenylene, hydroxy-C1-6-alkylidene, -O-, -S-, -O-alk-, -S-alk-, -alk-O-, -alk-S- or -alk-NR9-, where alk is C1-6-alkylene; n = 0-1; m = 0-1; addnl. details including provisos are given in the claims. Although the methods of preparation are not claimed, example prepns. and/or characterization data for 360 I and II are included. For example, III was prepared from by deprotection of tert-Bu 4-[4-(3-benzyloxypropoxy)phenyl]-3-[[[3-(3-methoxypropoxy)phenyl]methyl]oxy]piperidine-1-carboxylate, which was prepared by ether formation between tert-Bu 3-hydroxy-4-[4-[3-(2-methoxybenzyloxy)propoxy]phenyl]piperidine-1-carboxylate and 1-chloromethyl-3-methoxy-5-(3-methoxypropoxy)benzene using NaH in DMF.

IT 857273-93-9P, tert-Butyl (3R,4R)-3-[1-(3-methoxypropyl)-2-oxo-1,2,3,4-tetrahydroquinolin-7-ylmethoxy]-4-[4-[4-(3-methylindol-1-yl)butoxy]phenyl]piperidine-1-carboxylate 857281-01-7P, Benzyl (3R,4R)-3-[[4-(3-methoxypropyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]methoxy]-4-[4-[2-(3-phenylpyrrolidin-1-yl)ethoxy]phenyl]piperidine-1-carboxylate

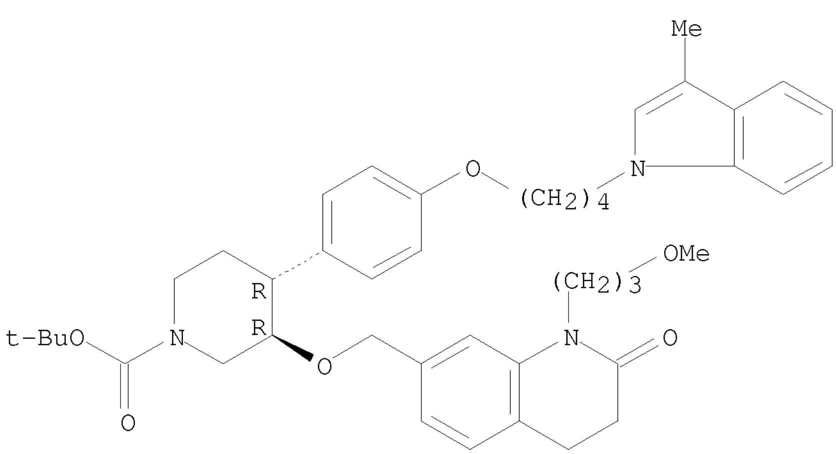
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of piperidines as renin inhibitors useful against hypertension and other disorders)

RN 857273-93-9 CAPLUS

CN 1-Piperidinecarboxylic acid, 4-[4-[4-(3-methyl-1H-indol-1-yl)butoxy]phenyl]-3-[[1,2,3,4-tetrahydro-1-(3-methoxypropyl)-2-oxo-7-quinolinyl]methoxy]-, 1,1-dimethylethyl ester, (3R,4R)- (CA INDEX NAME)

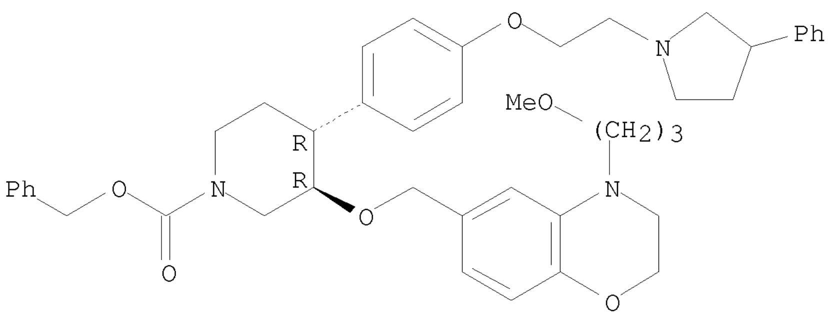
Absolute stereochemistry.



RN 857281-01-7 CAPLUS

CN 1-Piperidinecarboxylic acid, 3-[[3,4-dihydro-4-(3-methoxypropyl)-2H-1,4-benzoxazin-6-yl]methoxy]-4-[4-[2-(3-phenyl-1-pyrrolidinyl)ethoxy]phenyl]-, phenylmethyl ester, (3R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2004:878289 CAPLUS

DOCUMENT NUMBER: 141:366134

TITLE: Preparation of 4-(4-(heterocyclylalkoxy}phenyl)-1-(heterocyclyl-carbonyl)piperidine derivatives and related compounds as histamine H3 antagonists for the treatment of neurological diseases such as Alzheimer's

INVENTOR(S): Bamford, Mark James; Dean, David Kenneth; Wilson, David Matthew

PATENT ASSIGNEE(S): Glaxo Group Limited, UK

SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004089373	A1	20041021	WO 2004-EP3985	20040408
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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AU 2004228949	A1	20041021	AU 2004-228949	20040408
AU 2004228949	B2	20061102		
CA 2521899	A1	20041021	CA 2004-2521899	20040408
EP 1610786	A1	20060104	EP 2004-726514	20040408
EP 1610786	B1	20070620		
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BR 2004009110	A	20060328	BR 2004-9110	20040408
CN 1805747	A	20060719	CN 2004-80016195	20040408
JP 2006522771	T	20061005	JP 2006-505136	20040408
AT 365039	T	20070715	AT 2004-726514	20040408

ES 2288681	T3	20080116	ES 2004-726514		20040408
ZA 2005007795	A	20060726	ZA 2005-7795		20050927
IN 2005DN04435	A	20070928	IN 2005-DN4435		20050930
US 20060205774	A1	20060914	US 2005-551985		20051004
US 20060293298	A1	20061228	US 2005-246480		20051007
NO 2005005256	A	20060110	NO 2005-5256		20051109
PRIORITY APPLN. INFO.:			GB 2003-8333	A	20030410
			WO 2004-EP3985	W	20040408
			GB 2005-10731	A	20050525
			US 2005-551985	A2	20051004

OTHER SOURCE(S): MARPAT 141:366134

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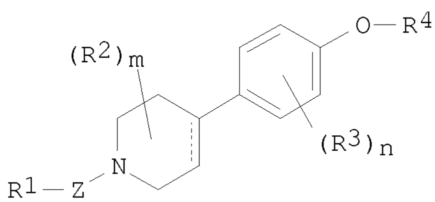

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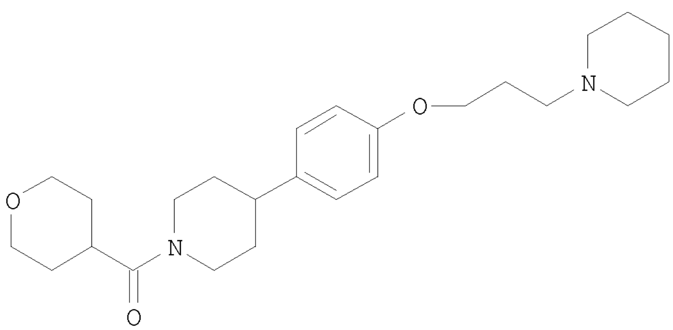


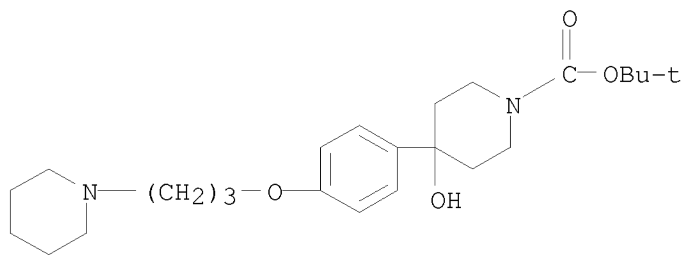
II

AB The present invention provides, in a first aspect, a compound of formula I [R1 = (un)substituted-C1-6alkyl-O-C1-6alkyl, -C3-8cycloalkyl, -aryl, -heterocyclyl, -heteroaryl, etc.; X = bond, O, CO, OCH2, CH2O or SO2; Z represents CO, CONR10 or SO2; R10 represents H, C1-6alkyl, -C3-8cycloalkyl, aryl, heterocyclyl, heteroaryl; m and n independently = 0, 1 or 2; R2 = H, C1-6alkyl or C1-6alkoxy; R3 represents halo, C1-6alkyl, OH, C1-6alkoxy, CN, amino, -COC1-6alkyl, -SO2C1-6alkyl or F3C; R4 = heterocyclyl or heterocyclylalkyl] or a pharmaceutically acceptable salt thereof, and methods to prepare I. Thus, e.g., II was prepared via amidation of 1-(3-{[4-(4-piperidinyl)phenyl]oxy}propyl)piperidine (preparation given) with tetrahydropyran-4-carboxylic acid. I and their pharmaceutically acceptable salts have affinity for and are antagonists and/or inverse agonists of the histamine H3 receptor and are believed to be of potential use in the treatment of neurol. diseases including Alzheimer's disease. I were tested in the histamine H3 functional antagonist assay and exhibited pKb values > 8.0.

IT 778642-43-6P 778642-48-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(intermediate; preparation or arylpiperidine derivs. as histamine H3 antagonists)

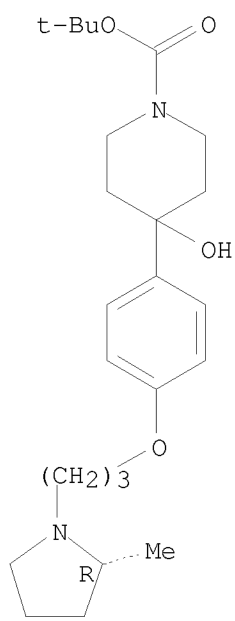
RN 778642-43-6 CAPLUS

CN   1-Piperidinecarboxylic acid, 4-hydroxy-4-[4-[3-(1-
     piperidinyl)propoxy]phenyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)



RN   778642-48-1 CAPLUS
CN   1-Piperidinecarboxylic acid, 4-hydroxy-4-[4-[3-[(2R)-2-methyl-1-
     pyrrolidinyl]propoxy]phenyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8   ANSWER 7 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2002:754196 CAPLUS

DOCUMENT NUMBER: 137:257677

TITLE: Methods of treating or preventing Alzheimer's disease using 4-aryl-3-aralkoxypiperidines and -azabicyclooctanes

INVENTOR(S): Nieman, James A.; Fang, Lawrence; Jagodzinska, Barbara

PATENT ASSIGNEE(S): Elan Pharmaceuticals, Inc., USA; Pharmacia & Upjohn Company

SOURCE: PCT Int. Appl., 449 pp. CODEN: PIXXD2

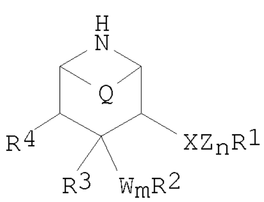
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002076440	A2	20021003	WO 2002-US9100		20020321
WO 2002076440	A3	20021128			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2002306848	A1	20021008	AU 2002-306848		20020321
US 20060079533	A1	20060413	US 2004-472868		20040202
PRIORITY APPLN. INFO.:			US 2001-278371P	P	20010323
			US 2001-308729P	P	20010730
			WO 2002-US9100	W	20020321

OTHER SOURCE(S): MARPAT 137:257677
GI

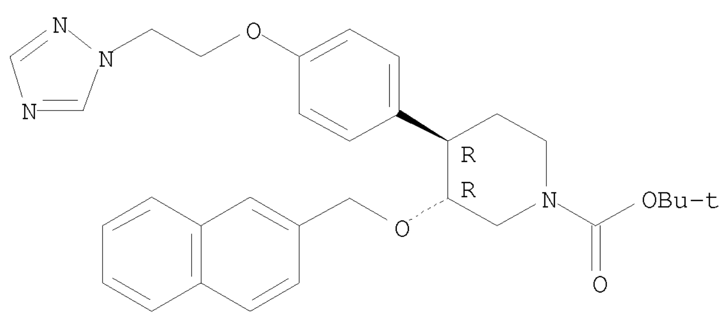


I

AB Disclosed are methods for treating or preventing Alzheimer's disease, and other diseases, and/or inhibiting β-secretase enzyme, and/or inhibiting deposition of A beta peptide in a mammal, using 3,4-disubstituted piperidinyl compds. (I) wherein the variables R1, R2, R3, R4, Q, W, X, Z, m, and n are defined below. Although neither the compds. nor the methods of preparation are claimed, .apprx.150 example prepns., translations from the German examples of patent WO 9709311, are included. I inhibit β-secretase with IC50 < 50 μM; compds. that are effective inhibitors of β-secretase activity demonstrate reduced cleavage of the substrate as compared to a control. In I, R1 is aryl, heterocycle; R2 is Ph, naphthyl, acenaphthyl, cyclohexyl, pyridyl, pyrimidinyl, pyrazinyl, oxopyridinyl, diazinyl, triazolyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, pyrrolyl, or furyl, optionally substituted. R3 is: H, hydroxy, lower-alkoxy, or lower-alkenyloxy; R4 is: H, lower-alkyl, lower-alkenyl, lower-alkoxy, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, benzyl, oxo, or where R3 and R4 together are a bond, or as specified in the claims. Q is: ethylene, or is absent; X is: a bond, -O-, -S-, -CH-R11- (R11 defined in claims), -CHOR9- (R9 defined in claims), -OCO, -CO-, or C:NOR10- (R10 is carboxyalkyl, alkoxycarbonylalkyl, alkyl or H), with the bond emanating from an O or S atom joining to a saturated C atom of group Z or to R1; W is: -O-, or -S-; Z is: lower-alkylene, lower-alkenylene, hydroxy-lower-alkylidene, -O-, -S-, -O-Alk- (Alk is a lower alkylene), -S-Alk-, -Alk-O-, or -Alk-S. N is: 1, or 0 or 1 when X is -O-CO; and where m is 0 or 1; with provisos. [This abstract record is one of 2 records for this document necessitated by the

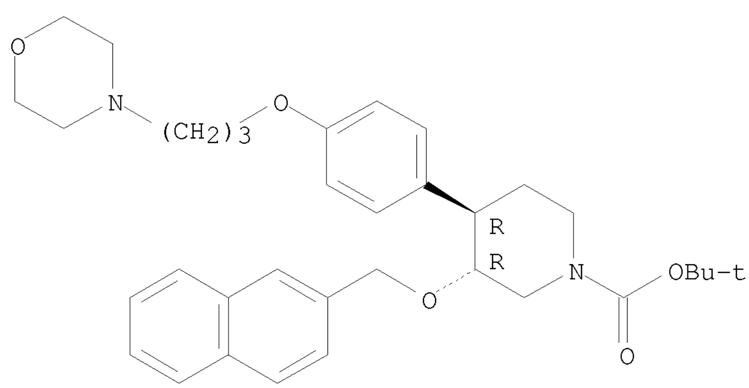
     large number of index entries required to fully index the document and
     publication system constraints.]
IT   188867-35-8P, 1-Piperidinecarboxylic acid,
     3-(2-naphthalenylmethoxy)-4-[4-[2-(1H-1,2,4-triazol-1-yl)ethoxy]phenyl]-,
     1,1-dimethylethyl ester, trans- 188867-78-9P,
     1-Piperidinecarboxylic acid, 4-[4-[3-(4-morpholinyl)propoxy]phenyl]-3-(2-
     naphthalenylmethoxy)-, 1,1-dimethylethyl ester, trans-
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (methods of treating or preventing Alzheimer's and other diseases using
        4-aryl-3-aralkoxypiperidines and -azabicyclooctanes)
RN   188867-35-8 CAPLUS
CN   1-Piperidinecarboxylic acid, 3-(2-naphthalenylmethoxy)-4-[4-[2-(1H-1,2,4-
     triazol-1-yl)ethoxy]phenyl]-, 1,1-dimethylethyl ester, (3R,4R)-rel- (CA
     INDEX NAME)

Relative stereochemistry.



RN   188867-78-9 CAPLUS
CN   1-Piperidinecarboxylic acid, 4-[4-[3-(4-morpholinyl)propoxy]phenyl]-3-(2-
     naphthalenylmethoxy)-, 1,1-dimethylethyl ester, (3R,4R)-rel- (CA INDEX
     NAME)

Relative stereochemistry.



REFERENCE COUNT: 3   THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8   ANSWER 8 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1997:307688 CAPLUS
DOCUMENT NUMBER: 126:277402
ORIGINAL REFERENCE NO.: 126:53775a,53778a

TITLE: New 4-aryl-3-aralkoxypiperidines and -azabicyclooctanes for treating heart and kidney insufficiency
INVENTOR(S): Binggeli, Alfred; Breu, Volker; Bur, Daniel; Fischli, Walter; Gueller, Rolf; Hirth, Georges; Maerki, Hans-Peter; Mueller, Marcel; Oefner, Christian; Stadler, Heinz; Vieira, Eric; Wilhelm, Maurice; Wostl, Wolfgang
PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
SOURCE: PCT Int. Appl., 492 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9709311	A1	19970313	WO 1996-EP3803	19960829
W: AU, BR, CA, CN, CZ, HU, IL, JP, KR, MX, NO, NZ, PL, RU, SG, TR				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
IN 1996MA01426	A	20050304	IN 1996-MA1426	19960813
CA 2230931	A1	19970313	CA 1996-2230931	19960829
AU 9667432	A	19970327	AU 1996-67432	19960829
AU 708616	B2	19990805		
EP 863875	A1	19980916	EP 1996-927715	19960829
EP 863875	B1	20030604		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1202152	A	19981216	CN 1996-197674	19960829
CN 1256326	C	20060517		
JP 11500447	T	19990112	JP 1997-510837	19960829
JP 3648251	B2	20050518		
BR 9610385	A	19990706	BR 1996-10385	19960829
HU 9900926	A2	19990928	HU 1999-926	19960829
HU 9900926	A3	20021228		
NZ 315677	A	20000228	NZ 1996-315677	19960829
RU 2167865	C2	20010527	RU 1998-106388	19960829
AT 242213	T	20030615	AT 1996-927715	19960829
IL 123293	A	20030624	IL 1996-123293	19960829
CZ 292327	B6	20030917	CZ 1998-684	19960829
ES 2201192	T3	20040316	ES 1996-927715	19960829
PL 193686	B1	20070330	PL 1996-325425	19960829
ZA 9607424	A	19970307	ZA 1996-7424	19960902
TW 474932	B	20020201	TW 1996-85110684	19960902
NO 310069	B1	20010514	NO 1998-954	19980305
US 6051712	A	20000418	US 1999-255185	19990222
HK 1016177	A1	20060901	HK 1999-101299	19990330
US 6150526	A	20001121	US 1999-456283	19991207

PRIORITY APPLN. INFO.:
CH 1995-2548 A 19950907
CH 1996-1876 A 19960726
WO 1996-EP3803 W 19960829
US 1996-711339 A3 19960906
US 1999-255185 A1 19990222

OTHER SOURCE(S): MARPAT 126:277402
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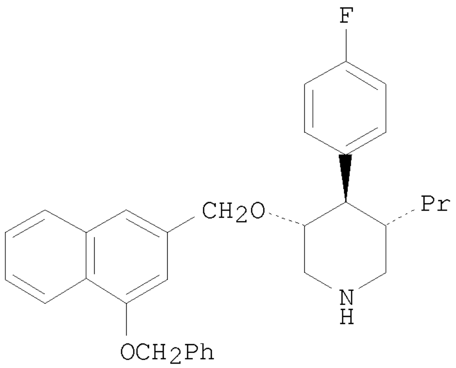


I

AB New piperidine and azabicyclooctane derivs. (> 1000 compds.) are renin inhibitors for treatment of high blood pressure, heart and kidney insufficiency. Thus, the piperidine derivative I was prepared from 1-benzyl-3-propyl-4-piperidinone by reaction with 4-FC6H4Br, followed by 1-benzyloxy-3-chloromethylnaphthalene and deblocking. I had a renin-inhibiting IC50 of 0.317 μM.

IT 188867-35-8P 188867-78-9P

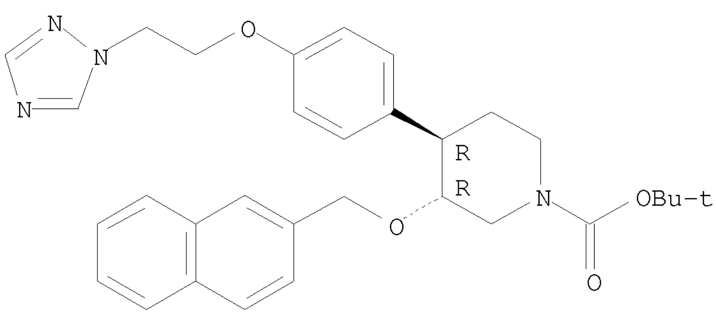
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of piperidine and azabicyclooctane derivs. as renin inhibitors)

RN 188867-35-8 CAPLUS

CN 1-Piperidinecarboxylic acid, 3-(2-naphthalenylmethoxy)-4-[4-[2-(1H-1,2,4-triazol-1-yl)ethoxy]phenyl]-, 1,1-dimethylethyl ester, (3R,4R)-rel- (CA INDEX NAME)

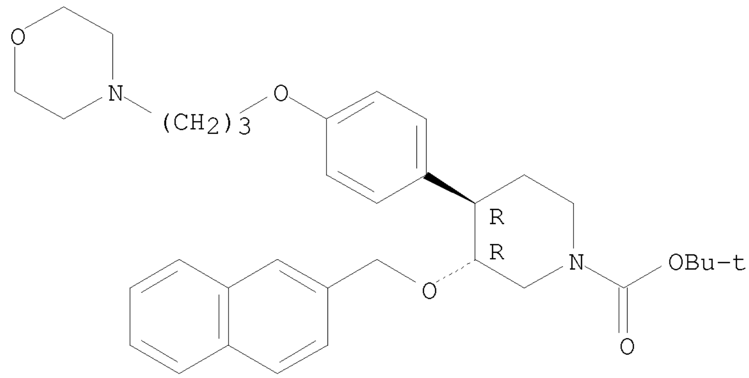
Relative stereochemistry.



RN 188867-78-9 CAPLUS

CN 1-Piperidinecarboxylic acid, 4-[4-[3-(4-morpholinyl)propoxy]phenyl]-3-(2-naphthalenylmethoxy)-, 1,1-dimethylethyl ester, (3R,4R)-rel- (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L2              3 S L1
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L4             10 S L3

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L5                STRUCTURE UPLOADED
L6              2 S L5
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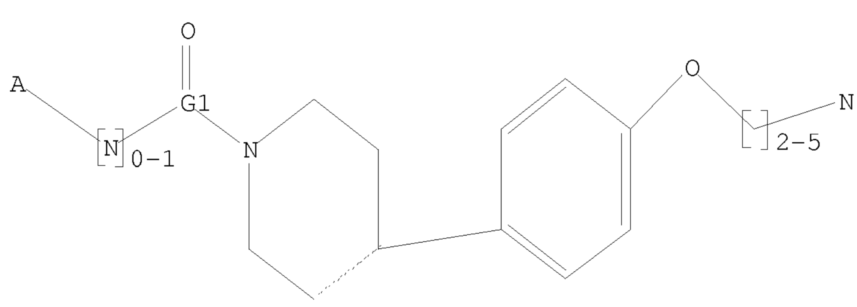

G1 C,S

Structure attributes must be viewed using STN Express query preparation.

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